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★ PROGRAM

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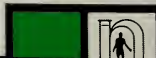
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# RELEVANCE

## *today and tomorrow*

# in Medical Education

### A FORUM WITH A PURPOSE

*There is a new and genuine concern in the world of education with what is called "relevance." The students of today question the relevance of much of their formal education as indeed do many of their elders. Students who are still in school question whether or not what they are being taught pertains to their needs as future citizens. In college the focus tends to be more upon the relevance of curriculum offerings to the realities of the world today and to such ultimate questions as the fundamental meaning of life and living, while in professional schools the concern is more with the relevance of the educational experience to the professional commitment in modern society.*

*The editors of CALIFORNIA MEDICINE propose to provide a forum in this journal for a discussion of "Relevance for Today and Tomorrow in Medical Education." Medical students, teachers, practitioners, administrators, government officials and the public are all deeply concerned that medical education be of high quality and that it be relevant to the role of medicine in the society of today and tomorrow. Just what is relevant and why it is relevant in the education of a young physician or the continuing education of an older physician is at present often a matter of individual opinion. It is a topic which deserves discussion.*

*The forum is initiated with statements beginning on the following page. Readers and others in California and elsewhere are invited to submit their views constructively and succinctly. As many of these as space permits will be published in future issues of CALIFORNIA MEDICINE as a continuation of this forum. At an appropriate time all the material will be collated and, if feasible, the distillate will be prepared in the form of a statement on "Relevance for Today and Tomorrow in Medical Education" for consideration by medical educators in California and elsewhere and by the Council of the California Medical Association.*

*There is an invigorating scent of change and renewal in the air at medical centers here and throughout the nation. This is an opportunity to contribute your views and perhaps help a little to stimulate the renewal and to shape the change.*

**EDWARD D. MARTIN**  
*Kansas City, Kansas*  
*University of Kansas School of Medicine;*  
*National President,*  
*Student American Medical Association*

AN ANALYSIS of the relevance of medical education might begin with the question: To what should medical education be relevant? If one accepts the Barzun model of the university, then medical education, as all education, is an end unto itself and the question of relevance becomes an internal one. To varying degrees, this has been the case in all medical schools and is epitomized by the endless faculty discussions on "How to Make the Basic Sciences Relevant to the Clinical Years" and "How to Make the Clinical Years Relevant to Basic Science."

This model, however, has become increasingly unacceptable to many individuals and there is a growing feeling that social institutions, including medical schools, exist as a mechanism for achievement of some larger goal of society. In the case of medical schools, the larger goal would seem to be the actualization of a health care system where adequate quality care would be available to all people in America and where health, not disease, would be the primary concern of health professionals.

Thus, one would assume that the health needs of the American people, in the broadest sense, is what medical education should be relevant to. The unique social role of the medical schools, then, would be the education of students in the basic skills, knowledge and ethic prerequisite for the practice of medicine in an evolving modern society.

One measure of the ability of medical education to fulfill its role might be the present health care crisis which, in large part, is a reflection of a health care system that cannot meet the needs and expectations of the American people. The medical schools which trained the physicians who exert significant influence within the present system clearly did not provide the knowledge, attitudes and insights essential for most physicians to deal with the profound social, as well as scientific, changes which are becoming characteristic of our

modern society. A denial of responsibility in this area by medical schools is unacceptable in the face of the evidence about the powerful socializing forces of medical education during which the basic learning and attitudinal patterns of future physicians are significantly shaped. Those in medical education who place the entire responsibility for the present problems on health care delivery upon the practicing physician are denying a basic cause-and-effect relationship.

The lack of concern, until recently, for community health, environmental health, and the behavioral sciences in medical schools has been well documented but this is secondary to the patterns of the rigid medical education process which have remained essentially unchanged since the Flexnerian revolution in medical education over 50 years ago. The almost pathological obsession many faculties have today with the "basic facts" and "scientific essentials" is a denial of the concept that education must be a process that develops individuals who are capable of continued and sustained learning and self-renewal in both the social and scientific realms. The educational approach of emphasizing the training of students to assimilate large amounts of knowledge and regurgitate it upon the proper stimulus is unrealistic in the context of a body of knowledge with a half-life of less than 5 years and which is expanding almost at a logarithmic rate.

The present model of the medical school as an isolated citadel of excellence in scientific and technical medicine will be difficult to change due to the ossification of the distorted research-education-service tripod of past years. With the billions of dollars that have been poured into research without balanced funding for education and service, it is hardly unpredictable that most medical centers would become sophisticated research and technical centers. The considerable increase in faculty size (540 percent between 1950 and 1966) is primarily a reflection of added specialists, researchers and basic science faculty with limited community practice experience; and this, too, has had profound effects upon the educational milieu of the medical schools. This is a reflection of the basic sources of funding emphasis for the medical centers. It is clear that increased funds specifically provided for medical education and related service will need to be made available to the schools.

It is now widely recognized and accepted that the traditional university relationship to the com-



munity will need radical changes. It is impossible to reconcile the acute, episodic and fragmented clinical service teaching system with either the needs of the community or the needs of medical students who will be practicing in a pluralistic and complex health care system. The higher purposes of education are served poorly when communities, usually poor, are exploited for "teaching material" with a minimal return in continuing comprehensive health care.

The problem of relevancy in medical education will only be solved when the medical schools recognize that their primary mission is to educate physicians who are capable of meeting the health care problems not only of today, but those which will arise in the future.

There is little disagreement that the scope of medicine and the responsibilities of the physician are expanding and changing at an ever-increasing rate. The previous forum in CALIFORNIA MEDICINE on this topic accentuated the magnitude of both the changes and the challenges. Medical schools are inextricably caught up in these changes and will need to develop the social and scientific sensitivity to appreciate the necessity of developing educational systems which are designed to produce physicians with new capabilities and a broader understanding of the scope of medicine. The artificial isolation of the university from the community must be replaced with educational systems working in realistic community clinical situations, the emphasis on informational content will need redirection with modern methods of educational process and problem-solving; and curricula will need broadening to include community and environmental health, medical economics, cybernetics, social engineering and related topics taught with an emphasis on the multidisciplinary team. Funding priorities will need substantial alteration to shift the emphasis of the university from research to education and service.

The medical profession is facing a growing number of challenges forced upon it by the increasing demands of society and its lack of adequate responsiveness in the past. A new approach to medical education is but one of these challenges, and the practice of medicine and the role that physicians will play in the future will depend, in large part, on whether the profession can aggressively and creatively find new approaches and solutions for the sizeable health care problems our nation faces.

**JOHN S. MILLIS, Ph.D., LL.D., Sc.D.,  
L.H.D., Litt.D.**

*Cleveland*

*Vice President, National Fund for Medical Education;  
Chancellor Emeritus, Case Western Reserve University*

I PREFER TO MAKE my contribution to the forum by responding to the question which is implicit in the title: Is medical education relevant for today and tomorrow? As a layman interested in medical education and as a consumer of medical care, I must give an ambivalent answer: "Yes" and "No." It seems paradoxical to describe an educational system as both appropriate and inappropriate. However, it is possible because the system of medical education is not the result of an intellectual and rational conceptualization. Rather, it is the evolutionary result of the impacts of independent and frequently conflicting forces. Dr. D. Joe Baughman\* has shown that the three major forces which have shaped medical education in the United States in each of its several eras are:

1. The form and character of medical practice.
2. The prevailing form of education.
3. The state of the sciences related to medicine.

The present system of medical education is largely shaped by two great successes and one failure. It is shaped by the irresistible force of the explosion of knowledge in the natural sciences, by the brilliant success of disease-oriented specialist practice in the care of critically ill patients, and by the failure to advance the science and art of education for the learned professions. The great increase in biomedical knowledge has produced remarkable increases in skill which in turn have made possible the diagnosis, the management, and, frequently, the prevention of many serious diseases and conditions. The practice of medicine has responded with a high degree of specialized competence and well-equipped hospitals in which seriously ill patients receive medical care of a character and quality which two or three decades ago would have been called miraculous. Because patients do suffer from serious disease and life-threatening conditions today and surely will tomorrow, that portion of

\*Baughman DJ, *Journal of Medical Education*, 33:2, February 1958

medical education produced by the force of an exploding science and a specialist practice model is relevant today and will be relevant tomorrow.

The weakness in medical education is not so much irrelevance but rather omission and incompleteness. The knowledge explosion has been uneven—earlier and more forceful in the natural sciences; later and as yet less forceful in the behavioral and social sciences. Thus, the added skills in the art of medicine have more frequently been those directly dependent on biology, chemistry, and physics than those dependent upon psychology, anthropology, or management science. While medical practice has developed brilliantly at the specialty level, there has been no comparable advance in comprehensive care, preventive medicine, or public health. To say it another way, medical practice has advanced a great deal for the 10 percent of patients who are critically ill but it has not advanced comparably for those parts of health care which affect most or all of the citizens of the country.

In choosing the university hospital for the exclusive environment of medical education, we have introduced substantial incompleteness. The environment is not one of comprehensive and continuing health care. The patients are more often desperately ill and less often seeking preventive care and health maintenance. The students' attention is concentrated upon disease rather than health, upon heroic intervention in desperate episodes rather than upon continuing surveillance of states of health. The institution is designed to render crisis care to the seriously ill without regard to cost, and is not a system for the delivery of health care to large numbers of people at a reasonable economic cost.

In my analysis, the most glaring weakness in medical education is the backward state of the science and art of education. We continue with a highly departmentalized system at a time when the frontiers between disciplines have disappeared. We continue with a horizontally segmented curriculum composed of pre-medicine, pre-clinical science, clinical science, internship, and residency when we desire to produce a whole physician equally at ease in science and in art. We continue with an educational lockstep when students are presenting a wide spectrum of talent, mastery of knowledge, motivation, and career expectation. We continue to stress teaching and to disregard the much more efficient process of self-directed learning.

Perhaps the simplest way to summarize the unevenness and incompleteness of medical education is to point out the unevenness of our support of research in the three areas which largely determine the system. We are spending billions of dollars a year in biomedical and specialty-oriented clinical research, perhaps a few millions in research in medical education, and a few hundreds of thousands in research in the delivery of medical care. We have produced great strength in the area of science, strength in one part of medical care, and have been content with the status quo in education and in large areas of the delivery system of health care.

**PAUL J. SANAZARO, M.D.**

*Bethesda*

*Director, National Center for Health Services Research and Development, Health Services and Mental Health Administration, Department of Health, Education, and Welfare*

THE SCOPE AND RESPONSIBILITY OF MEDICINE, as defined jointly with society, are the basis for judging the relevance of medical education. If this general view is correct, the definitions of scope and responsibility which were published some months ago in these columns could constitute the criteria for judging whether medical education of today and its likely next stage are relevant.\* I believe that those formulations are sufficiently apt, accurate and comprehensive to serve as a basic point of reference.

There are of course other aspects of relevance. First, the scope of medicine is actually the aggregate of all efforts by all physicians and medical scientists and those who work with them and on their behalf. But many faculties today are exhibiting their sense of relevance by focusing more and more upon the academic needs and professional and scientific interests of individual stu-

\*Watts MSM: The scope and responsibility of medicine—A statement drawn from contributions to a forum. *Calif Med* 109:509-514, Dec 1968



dents. Individualization of curriculum content, emphasis and duration is the watchword and properly so. All of this may not add up to a relevant whole.

At this time, many medical schools and teaching hospitals are struggling to give academic respectability to the term "community medicine," for they recognize that serious engagement here is also a *sine qua non* of relevance. It will require a number of years and much more involvement of other health professions and academic disciplines before community medicine generally acquires distinctive academic characteristics.

Another issue has to do with the shift in national priorities as they affect Federal support of research. We see today a crescendo of social and political action directed to attainment of equal access to quality care for all our people, especially those who are most disadvantaged and at greatest risk. Because of competing demands for the limited number of dollars, Federal support of basic biomedical research has leveled off. But this should not be interpreted to mean that such research is no longer considered relevant. Medical schools must continue to attract the finest minds to such work and to place priority academic emphasis on basic research. The reason for this is self-evident: It is this very research and only this research which gives meaning to the current exhortations to emphasize preventive medical practice. Greater efficacy of preventive medicine has always been a much to be desired goal. Its value is amply demonstrated in many fields of medicine. But as of today it is far from being able to alter the course of a vast majority of the important biological and psychological illnesses. It is only through continuing basic and clinical research that we can realize a greater proportion of the ideal of prevention.

Relevance, like beauty, is often in the beholder's eye. Medical students often see relevance in tangible evidence that their faculty is concerned about the plight of the socially and economically disadvantaged who also suffer from lack of care. Some students see relevance in those activities which give students a voice and a vote in decisions ordinarily reserved to the faculty or the dean.

In the eyes of individual faculty members, individual deans, individual regents and individual university presidents, relevance is defined in many different ways. Many of these will seem contradictory, yet each alone may be equally rational and

justified. But only on the national aggregate of such perceptions should the judgment of relevance be made. It is not likely that one school or one university can exhibit all the relevance that society, or even medicine, might desire.

The most distinctive aspect of needed relevance in medical education is only beginning to emerge. If it can (could?) be encompassed in the present and emerging patterns of medical education, medicine will have entered a new dimension of social responsibility. It is no longer news to anyone that the current turmoil in social policy will result in new forms of medical practice, different methods of payment, a change in the overall organization of medical care and a different set of relationships among medicine, government, and other public and private institutions. These changes will occur because of initiative and responsiveness by physicians. Currently, medicine is only one participant among many other equal institutions in this evolutionary social dislocation. What it requires if it seeks the advantage of leadership is a cadre of physicians and health professionals educated in the disciplines and methods for objectively analyzing the issues and problems of medicine in relation to the changing social policy.

Such education needs to begin at the undergraduate level, to assure this capability in the next generation. It can and should include training during residency years. But if organized medicine is to influence the immediate future of medical care, it needs the services of these new medical statesmen very soon. Special forms of continuing education are the only recourse.

As a result of their additional training, these men will have to acquire a deep understanding of medicine's relationships to other social institutions and political and economic processes of our nation. They will also have to learn the capabilities and limitations of diverse disciplines for contributing to the resolution of problems in the organization, delivery, quality and financing of medical care specifically and health services generally.

Stated more simply, medical education is challenged to create and collaborate in the creation of the new disciplines and new careers basic to a productive attack on socio-economic and political issues as they affect and involve medicine. When these take their place beside molecular biology and the rekindled concern for excellence in patient and community care, medical education will have found the secret of continuing relevance.

S. ALEX STALCUP, A.B.

*San Francisco  
President, Associated Students, University of  
California, San Francisco Medical Center*

THE MOST ACCURATE EVALUATION which could be made of medical education is the very basic contention that much of what passes for medical education today is irrelevant. This point of view is based upon a pessimistic perspective on the current world situation: over population, impending famine, environmental pollution, racism, poverty, war, and violence. Most of the disease which is treated by the present products of medical education is derived from these very basic problems.

The health profile of an individual may be viewed as a wide continuum, ranging from "health" through "disease" with environment (as delimited by the problems listed above) as the factor which decides where an individual will be placed on the continuum. Present medical practitioners are trained to intervene in this process at the "disease" end of the continuum—after the negative influences of imbalanced ecology have wreaked their destruction. My contention is that we are training the wrong type of doctors: "death specialists" — interventionists at the wrong end of the continuum. Considering the apparently accelerating pace of ecological and societal disintegration, we are placed in an absurd race to produce more "death specialists" while the environment produces rapidly increasing numbers of victims.

If the resources now being allocated to medical education, hospital construction, and some basic sciences research were diverted into basic ecological research and environmental control, the need for ever increasing numbers of the present type of health professionals would decrease. I envision a new type of health practitioner who would supplant the physician and render him obsolete. This new practitioner would function at the "life" end of the health-disease continuum, serving as a physician to the environment, doctoring the ills of multiple ecosystems. There would, of course, continue to be a place for the disease specialists, to manage those who are essentially treatment failures of the health specialists.

What does this mean in the context of the reality of present medical education? I believe that medical students, like those who preceded them, are being trained to treat symptoms of disease and given little insight into the processes which produced the disease. We treat cirrhosis of the liver instead of Skid Row, lead poisoning instead of slum landlords, and pesticide toxicity instead of grape growers. Viewing the steady pace of environmental degeneration, we will inevitably be subject to chronic shortages in adequate physician manpower; as long as the basic agents of disease are allowed to persist, there will continue to be an insufficient number of physicians.

We must reorganize medical education to provide for an emphasis on the normal and desirable in a healthy system. Medical students are refusing to remain silent on the present ordering of the nation's priorities. Our education must provide for aggressive, activist advocacy of patient welfare, including total absorption in the pursuit of strict environmental control, equality of opportunity, and peace.

The symptoms of our presently misplaced effort are reflected in the inefficiency of the present model of health care delivery, the doctor-patient interaction. The effect of the pyramidal hierarchy within the hospital (students at the bottom, senior staff in the academic ionosphere) is to infantilize the student and invalidate the years of valuable education and insight which he brings to the medical setting. Fresh from the "outside world," the entering student in medical school is probably a much finer physician (as proposed above) than the aging clinical genius of ward-rounds fame. The entering student is the product of the broader experience and broader perspective of contemporary culture—as yet not forced to develop the tunnel vision of disease-oriented super-specialists in pursuit of signs and symptoms.

My plea is for the enhancement of the freshness and breadth of vision possessed by the entering student. There is an immediate need for the inclusion of sociology, Black history, economics, psychology and anthropology into the basic science core curriculum. The development of "urban health specialists," "ghetto medicine specialists," "population and nutrition specialists," and "environmental hazards specialists" would be the actualization of the plea for relevancy of a growing segment of the current medical student population.



**GLEN R. LEYMASTER, M.D.**

*Philadelphia*

*President (formerly Dean and President),  
Woman's Medical College of Pennsylvania;  
Chairman, Advisory Committee on Undergraduate  
Medical Education, American Medical Association*

BEFORE ME LIES THE RECORD of a Faculty-Student Workshop on Curriculum, held at my medical school a few months ago. Throughout the discussion, the prevailing theme is *relevance*. Why are programs not relevant? How to make them so? What is relevant?

These questions have been asked for years, but the few faculty and student voices were weak and timid. The voices in every school now are louder, even strident. The urgency originated with the students although faculty are increasingly echoing their concern.

What is relevance in Medical Education? What are the students saying to us?

I have tried to listen carefully. I think I perceive two main ideas, two pleas: (1) "Teach us skills and knowledge that we know we will use, give us *practical* training," and (2) "Help us acquire knowledge, skills and attitudes that will enable us to serve all of the health needs of all of society, more completely and more humanely than we see our elders doing."

The first deserves only brief comment. It is the recurrent cry of the impatient student. A generation ago, the term was "cold dope." Nothing has proved less enduring than most of those practical gems of knowledge we learned years ago. Fortunately, few teachers are so responsive to flattery or so egotistical that they will try to identify that which will be useful several years hence. Students are, in the main, perceptive enough to know that the lifelong task of acquiring and refurbishing practical skills is theirs, and theirs alone.

The second area is far more important. While not new, demand for relevance by so many students is a significant modern development. Too observant to miss the obvious, too concerned to keep silent, and too brash to be respectful, they are being heard. Already they have begun to affect the content and process of medical education.

The music of Rock seems often obscured by the

noise. For the same reason their ideas do not always come through clearly. I hear these:

- "Let us be more involved in our education. Allow us to help decide what we need to learn, and especially how we go about it. We will learn those things pertinent to our destiny. We want not to repeat your sterile experiences just because you went through them."

- "Give us opportunity to prove for ourselves that the science you want us to learn is relevant. Allow us to test its pertinence early in our medical school career, with patients, with social problems, with community experiences. Don't teach us to be scientists and then tell us not to question your statements about its importance to us."

- "We see in our hospitals, in our clinics, in doctors' offices real evidence that medicine is too often heartless to the individual and heedless of public needs. We see a dedicated, hardworking profession using costly, precise instruments, but we see them working in such a chaotic non-system that indefensible inequities to the poor, to the isolated, and to the unlucky often result. Why can't a society that can put a man on the moon put elementary medical care into the ghetto?"

- "We think you may have unbalanced the humanity and the science of medicine. We see too many patients enter our hospitals and clinics unhappy, frightened and undiagnosed, and leave them diagnosed—but unhappy and frightened. You tell us a patient's feelings are important but you study only his body. Why can't a profession capable of transplanting hearts do a better job of relieving anxiety and fear?"

These are discerning and discomfiting comments on today's scene, and merit a thoughtful response. It will not do to say that the students are too inexperienced to know the answers. Probably, we demonstrate that by the time we get the experience to learn the answers we have forgotten the questions.

**BURT L. DAVIS, M.D.**

*Palo Alto*

*Trustee, American Medical Association;  
Past President, California Academy of  
General Practice*

THE PROBLEMS OF MEDICAL EDUCATION of today and tomorrow are complicated by (1) accelerating scientific knowledge, (2) the population explosion,

with ever increasing manpower needs, (3) changes in the structure of society which require a wider variety of health delivery systems, (4) computer application, not only in history retrieval, diagnosis and therapeutics, but also in the compilation and collation of sociologic and economic data pertaining to health care, and (5) the increasing interest and activity of students in a broad spectrum of education, with a desire for social, economic, and political studies to be introduced into the curricula of medical schools.

Society has developed an insatiable thirst for health care. Many programs have been formulated. Unfortunately, many of these plans, although well intentioned, have only served to add to the increasing demand for universally available health care of high quality.

It is obvious, that medical schools are unable to respond quickly enough to meet these demands, even though many medical schools have been created recently or are being created at present. Nevertheless, there is a time lag between planning, fund raising, designing, faculty organizing, and the admission of students, who then will have 4 years of medical school, plus years of postgraduate training before entering practice.

There is no single solution for these problems. They are all interrelated. They all require simultaneous solutions. There must be a multi-pronged attack in which the medical profession is obliged to seek solutions so that it can assure the American public that it will have medical care of high quality at a reasonable cost.

The most vigorous antagonists of the medical profession and of the present system of health delivery focus on only one or two of these problems. It behooves the medical profession, with its expertise in this field, to develop new methods of delivery compatible with our present system. In the training of doctors of medicine, the curricula must be studied, evaluated, and redesigned, in order to produce logical and effective mechanisms. To suggest a few:

1. Two-year medical schools to provide laboratory facilities and to relieve the 4-year schools from the burden of having to have a tremendous amount of space and capital allotted for this purpose would seem to be within the province of any well run recognized university. Departments of biology, chemistry, physics, physiology, of most universities could be augmented with slight additional costs. These universities might then be able

to introduce the other basic components of anatomy, bacteriology, et cetera.

2. The 4-year school curriculum could be redesigned to make more hours available for basic introduction to economics, sociology and political science.

3. The tendency toward specialization has increased the number of full-time faculty, so that in some university medical schools students are not exposed to practicing physicians who might well give them practical advice on the problems of practice in other than medical school setting.

4. "Lengthen the physician's arms" by the use of trained personnel in specific fields, similar to the use of medical corpsmen in the services. A few medical schools and a few county medical societies have experimented in this; and, although the number of such trainees has necessarily been small, they have given promise of being highly successful. It is not enough, however, to train a medical corpsman, physician's assistant (or, possibly more properly, assistant physician), feldsher, laboratory technician or nurse to assist the physician and thus release him for the important work for which he has been trained. In order to make any of these vocations attractive, there must be opportunities for advancement. This means that the basic training for these assistants must be the same as the basic training for a physician, and although they step out of the elevator at a different floor level, there must be an acceptable method whereby the well motivated and ambitious members of these groups can, with supplementary training, elevate themselves and ultimately become fully licensed doctors of medicine. This is going to mean supplementary training courses produced by medical schools and by hospital staffs and will take considerable revision of our thinking and planning.

A closer relationship between medical schools, their students and their faculty and the practicing physician is an absolute "must" in order to release the energy which will be required to fulfill the manpower requirements.

The application of computer technology to medical practice, while still in its infancy, has great effect upon our delivery system. The advance in this regard can be appreciated by considering that had the Truman Administration, 20 years ago, been able to put forward its pet form of prepayment, the means then available for record-keeping and the processing of claims would have been wholly inadequate in light of what we now know about the



tremendous load of claims that has been produced by increased desires and population. With 130,000 claims a day being processed by California Blue Shield, it has been necessary to add to computer ability, increasing amounts of capacity and sophistication. At least a basic knowledge of computer operation, then, will be required for tomorrow's medical education. The validity of answers obtained from the computer is dependent entirely upon the quality of information that is placed within it.

Medical education is being asked to do more than any other professional type of training. It is being asked to fulfill its primary functions of training capable physicians, and increasing research to broaden and apply medical knowledge. In addition, it is presented with social questions which have become increasingly dominant and for much of which no one has the answers. This is not true of other professions. Certainly not to as great extent as it is true in medicine. New techniques are being developed, and these are expensive. Only one of nine persons who could be assisted by artificial kidneys can be provided with the treatment, because the large capital expenditures that are necessary make universal availability of the equipment economically impossible.

Society has become increasingly concerned because it wants universal application of the utmost of medical skill and scientific acumen. It is demanding that medicine involve itself in problems of the ghetto, problems of the poor, and in a variety of relatively unknown areas, but in which a high degree of emotion exists.

What is relevant in medical education today, and what will be relevant in medical education tomorrow? Medical education must be designed to fit the student for practice in tomorrow's world. Twenty-five years from now, almost every physician who is now over 45 years of age will not be in practice. Therefore, it is the present student group and the doctor who now is under 45 years old who bears the greatest responsibility to formulate the type of practice in which he wants to engage. The world is changing and medicine is changing, and not all of the change is bad. Medical societies are inviting medical students to participate in their committee work. The Colorado Medical Association has recently established a component chapter at the University of Colorado Medical School which will have all of the rights and privileges and prerogatives of any county society within the state, including the

right to elect delegates to sit in the house of delegates of the Colorado Medical Association.

The California Medical Association established the Scientific Board in order to make closer ties with those physicians in the academic community.

The answer to the questions posed above may be summed up in two words: *concern* and *involvement*—concern for the needs of the American public, scientific, economic, sociologic, and political as well as medical; involvement, in order that concern may be directed by the only profession which has the background, knowledge, acumen and experience to direct actively this concern into the production of a broadly based multi-faceted health delivery care system, applicable to all portions of our society.

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WHEN THE ACTIVIST enters medical school these days and starts to demand that the curriculum be relevant, one almost gains the impression that he really is asking that there be change, change for change's sake alone. Relevance, however, means pertinence or applicability, which casts a rather different light on the whole problem, for change in these terms must be pertinent, that is, pertinent to the goal of medicine. Today it is pretty generally accepted that every citizen has a basic right to have access to quality health services (or as I prefer to define it, every citizen has a right to expect appropriate health services to be available to him at an attainable cost). In these terms, therefore, it seems entirely reasonable that medical education should be relevant (pertinent) to the attainment of this goal.

When one examines in detail what medical education must provide students if they are to be prepared to meet this goal, one finds that material must be offered from several widely separated areas of activity: (1) Students should have first-hand

experience with providing health services in a variety of settings, (2) Students should be exposed to the processes of scientific thought and advancing knowledge, *i.e.*, research at both basic science and clinical levels, and (3) Students should have some contact with the disciplines and problems encountered in teaching and administration. Intimately interwoven throughout all these experiences must be not only the scientific knowledge (basic as well as clinical) which is mentioned above, but also the knowledge of sociology, anthropology, political science and economics (practical as well as abstract)—a tremendous task, but a necessary one, if students are to learn how to provide service in an acceptable guise, as well as how to help patients know what to expect from such service, and how to get what they need and want.

There are a few additional items which have to be included somehow in this package which will help to ensure that medical education is relevant. First, medical education has a responsibility to teach and to demonstrate the scientific approach to social problems affecting health, not to permit these problems to be approached simply on an emotional basis. Next, in addition to the scientific aspects catalogued above, it is to be hoped that students who emerge from such a training process will have developed an *esprit* which will lift them a notch or two above the average citizen in accepting their responsibility to work for the betterment of society. (It has to be remembered that the exercise of such civic responsibility carries with it the duty not only to help society effectively and realistically meet its obligations to its members but also to appreciate how social changes are wrought in a timely and constructive manner.) Last, if medical education is to be truly relevant, it must impart to students the concept that physicians must be lifelong students. Physicians in training must be exposed to methods (and ideas) for keeping abreast of the scientific advances and social requirements of tomorrow. Anything less than this will leave them technologically and philosophically obsolete.

In summary, then, medical education should be, indeed must be, relevant. This means students must be exposed adequately not only to scientific facts and their application, but also to scientific approaches to society's and people's problems in the health fields. In the process, it is to be hoped that physicians will gain an *esprit* which will enable them to be effective, responsible citizens and lifelong students in a changing and challenging world.

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I UNDERSTAND the topic chosen for this forum to raise two questions: (1) How is medical education relevant for decisions we have to make today; and (2) How is medical education relevant to the needs, problems and opportunities of the future? I respond to these questions in broad terms because this is all that time and space permit.

The overweening issue of our time is the absorption of modern technology into the framework of human purpose. Technology has yielded material abundance, weapons of war and the conquest of inner space. It has made its contribution to the control of disease as well. It has so far contributed much less to the relief of human anxiety in a rapidly changing world. Many people believe that in this dimension technology has been far more negative than positive in its net effects. The current mood in many quarters is to reject both technology and the sciences that give rise to it. The consequences of this rejection would be a return to obscurantism and witchcraft.

Modern medicine increasingly harnesses science and technology, and in a context of human concern. Young people who turn away from physical science and technology often are attracted to biological science and biotechnology. Where agriculture was the chief practical manifestation of biotechnology in the past, medicine has now equalled and probably surpassed it. Those of intellectual bent who seek a practical payoff with an emotional twist, can find it in medicine. Medical education is relevant to the decisions students are making today because it provides an outlet for practical idealism, and a constructive alternative to personally directionless revolt.

Curiously, and unhappily, this comes at a time when decisions in another arena are being made in another direction. It is fair to say that national policy in the past decade has paid lip service to medical education but is failing to follow through. Budgetary cutbacks in Washington are hitting the health sciences just as the effort to increase physi-

cian output is getting off the ground. Like the two faces of Janus, health sciences and health education are closely interrelated, the one cannot decline without affecting the other. The quality of physicians is a function of medical knowledge, and medical knowledge must move forward with our changing times. Whatever the successes of suburban medicine today, it has not been, and cannot be, adequate for current central urban problems—or for the approaching problems of high density medicine in, for example, Latin America or Africa.

Here we merge into the second question, medical education in relation to the decisions of the future. One thing that characterizes all education—and medical education particularly—is that it is *always* for the future. Most of the members of our entering medical class this year will begin independent practice as we turn into the last quarter of the 20th century, and most will be leaders of their profession in the year 2000. What will medicine and the world be like at midpoint in their careers, say 1990? Will physicians at that time still be merely placating disease, or will they be working aggressively out into the community and the environment as leaders of

health teams? Will health professionals establish standards for physical construction and planning, whether of buildings, communities or cities? Will biotechnology be followed by psychotechnology, and this in turn by social engineering? Will the physician become the teacher and conductor of health living? To what extent will the medical education of today determine these questions by the kind of physician it produces? Could anything be more relevant for tomorrow than the opportunity to influence that?

In these terms medical education is as relevant for today and tomorrow as is the assessment of, and an effort to improve, the condition of man, now and in the future. The anguished cry of the ghetto of today, and the suffocated screams of tomorrow's black holes of Calcutta, assure relevance. It has always been relevant to train those who minister to the sick and bind up the wounds of the injured. Today's relevance goes beyond even that. It is the relevance of the possibility that present human concern can become a prime determinant of the future condition of man.



# Genetic Variants of Hemoglobin and Other Blood Proteins in the San Francisco Bay Area

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■ *Studies of blood genetics in "normal healthy" persons and patients of different racial groups in the San Francisco Bay Area were carried out from January 1965 to April 1968. They show that diseases due to genetic abnormalities of blood are fairly common in this region. Frequencies for abnormal hemoglobins and erythrocyte enzyme deficiencies and variants were recorded and it was noted that abnormalities in hemoglobin metabolism that may lead to mild or severe clinical and hematological symptoms proved rather common. Accompanying other disease conditions, they may cause difficulties in diagnosis. Several diseases due to or associated with different enzyme abnormalities were encountered.*

THE MULTIRACIAL population of the San Francisco Bay Area offers an unusual opportunity to study polymorphism and inherited blood abnormalities. Recent developments in the study of abnormal hemoglobins, inherited erythrocyte enzymes and serum proteins focus attention more and more on blood as an important and easily obtainable tissue for studying the functions and interactions of genes and gene abnormalities.

This paper reports some results of investigations carried out in San Francisco from January 1965 to April 1968. It presents frequencies for such well known genetic traits as hemoglobins S and C and glucose-6-phosphate dehydrogenase (G-6-PD) deficiency. The frequencies are known for many

areas of the United States but have not previously been published from San Francisco and environs. Results also indicate that diseases due to genetic abnormalities of blood are fairly common in this region.

## Materials and Methods

Blood was obtained from 404 "normal healthy" persons (doctors, students and other personnel at the University of California Medical Center) and from 1,355 patients of the University hospitals and the Chinese Hospital in San Francisco. Specimens were also obtained from patients admitted to the University of California Medical Center and from those referred for consultation from other Bay Area hospitals.

Hematological studies followed standard methods, and special studies were carried out as indicated.

*Abnormal hemoglobins.* Electrophoresis for hemoglobin patterns was performed by the method of Smithies<sup>1</sup> in starch gel and of Robinson et al<sup>2</sup> in

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TABLE 1.—Frequency of Abnormal Hemoglobins in Different Racial Groups in the San Francisco Bay Area

Race	Healthy Persons				Patients				Healthy Persons + Patients			
	No. Normal		Abnormal Trait Carriers of Hb		No. Normal		Abnormal Trait Carriers of Hb		No. Normal		Abnormal Trait Carriers of Hb	
	S	C	B <sub>3</sub>	J	S	C	B <sub>3</sub>	HPP	S	C	B <sub>3</sub>	HPP
Caucasian	122	122	..	..	709	707	..	..	831	829	..	1
Negroes	133	113	14	4	469	403	49	9	602	516	63	1
					(10.4%)	(1.9%)	(1.5%)	(0.2%)	(10.5%)	(2.1%)	(1.5%)	(0.2%)
Filipino	144	144	..	..	14	14	..	..	158	158	..	..
Chinese	5	5	..	..	115	115	..	..	120	120	..	..
Miscellaneous					48	48	..	..	48	48	..	..
Total	404				1355				1759			

HPP = Hereditary persistence of fetal hemoglobin.

agar gel. Alkali-resistant hemoglobin was estimated by the method of Singer et al.<sup>3</sup> The acid elution technique of Kleihauer and Betke<sup>4</sup> was used to show fetal hemoglobin; solubility studies were made by the method of Itano<sup>5</sup>; quantitative analysis of hemoglobin was made by the chromatographic method of Huisman and Dozy.<sup>6</sup> Polypeptide chains of hemoglobin were studied on starch gel electrophoresis in a urea-barbital system at pH 8.0 (Chernoff and Pettit<sup>7</sup>). Peptides were "fingerprinted" by Baglioni's<sup>8</sup> modification of Ingram's<sup>9</sup> method. Isolated peptides were hydrolyzed in 6 N.HCl and analyzed on a Beckman Spinco automatic amino acid analyzer (Model 120C).

## Enzymes

Screening for G-6-PD deficiency followed the method of Motulsky and Campbell<sup>10</sup>; analysis of G-6-PD electrophoretic types, the method of Shows et al<sup>11</sup>; and quantitative estimation of G-6-PD activity, the method of Marks.<sup>12</sup> *Carbonic anhydrase* isozymes were examined by the method of Haut et al<sup>13</sup> and Tashian and Shaw<sup>14</sup>; quantitative estimation of carbonic anhydrase, by the method of Wilbur and Anderson.<sup>15</sup> *Catalase* was estimated by the method of Vella,<sup>16</sup> but adjusted for a hemoglobin level of 14 grams per 100 ml. Electrophoretic patterns were examined by the method of Tudhope.<sup>17</sup> *Phosphoglucomutase* (PGM) isozyme study followed the method of Spencer et al.<sup>18</sup> *Pyruvate kinase* activity was assayed by the method of Tanaka et al.<sup>19</sup> *Alkaline phosphatase* was studied by starch gel electrophoresis and specific staining according to Boyer.<sup>20</sup> *Lactate dehydrogenase* (LDH) isoenzymes were examined according to Kraus and Neely.<sup>21</sup>

## Results and Discussion

### Frequency of abnormal hemoglobins by race

Table 1 presents frequencies for the 1,759 "normal healthy" persons and patients, excluding patients referred for consultation. Although these normal persons and the patient groups are not truly representative of the general population, the results throw light on the frequencies of blood abnormalities in various racial groups and in patients seeking medical treatment.

*Caucasians.* As expected, abnormal hemoglobins were rare; only two of 831 in this group were trait carriers. One had a fast-moving hemoglobin with the mobility of Hb J at pH 8.6, shown by polypep-

tide chain study to be an  $\alpha$ -chain abnormality. Further structural studies could not be made for lack of blood and patient cooperation. The second trait carrier, an Armenian, had a slow-moving hemoglobin with the mobility of Hb G on electrophoresis at pH 8.6. Structural studies thereon are not yet completed.

**Negroes.** In this group the frequency of Hb S trait carriers was 10.5 percent, falling within the range for Negroes in the United States as reviewed by Livingstone.<sup>22</sup> Dr. Nicholas Petrakis of the University of California Medical Center, in a preliminary study of abnormal hemoglobins in the general population, found the Hb S trait in Negroes more frequent in children than in adults (personal communication). The frequency for Hb C seemed about the same as in the eastern part of the United States, where Smith and Conley<sup>23</sup> reported 1.8 percent in 500 Negroes examined. The frequency for Hb B<sub>2</sub> (a delta chain abnormality) was 1.5 percent, also within the range Livingstone<sup>22</sup> noted for Negroes in the United States. As elsewhere, hereditary persistence of fetal hemoglobin was rare in the Negroes sampled in San Francisco and was not found in any other racial group in this study.

#### *Abnormal hemoglobin with clinical and hematological symptoms*

Thirty patients whose hemoglobins were abnormal consulted their physicians because of weakness or anemia. Table 2 lists the kinds of hemoglobinopathy responsible for clinical and hematological signs in 26 patients and the abnormal hemoglobins accompanying unusual conditions in three others.<sup>24,25,26</sup> Another patient's condition, not included in the table, was noteworthy because it showed the interaction of Hb Q with another hemoglobin abnormality that could not be further defined because the patient died.

Besides these 30 patients, 27 persons with mild anemia had  $\beta$ -thalassemia minor. Most of these thalassemia trait carriers, all adults with mild anemia of obscure origin, were referred from outpatient departments. Five, however, were sent to us for diagnostic confirmation of the  $\beta$ -thalassemia trait. Ten of the 27 trait carriers were Italian, seven Greek, and four Negro; one each was Italian-Irish, Italian-British, Chinese, and Indonesian; two others were labeled "Caucasian."

Clinical, hematological and biochemical findings for the eight patients in Table 2 who had sickle-cell anemia suggested that it was homozygous, but a

TABLE 2.—*Types of Hemoglobinopathies Associated with Clinical Symptoms*

Type of Hemoglobinopathy	Number	Race
Sickle-cell anemia	8 unrelated	Negro
Hb S — $\beta$ thalassemia	2 unrelated	Negro
Hb S — C disease	2 unrelated	Negro
Hb S — B <sub>2</sub> disease	1	Negro
Hb S — G Philadelphia	3 (in 1 family)	Negro
Hb C — disease	2 unrelated	Negro
Hb B <sub>2</sub> — $\beta$ thalassemia	1	Negro
Hb H — disease	7 (in 4 families)	3 Chinese 2 Filipino 2 Filipino-Mexican
<i>Abnormal hemoglobin associated with unusual conditions.</i>		
Persistence of Hb F with carbonic anhydrase deficiency and low Hb A <sub>2</sub>	1	Greek
Hb S trait with carbonic anhydrase deficiency and increased Hb F	1	Negro
Hb J trait with macroglobulinemia and increased Hb F	1	Caucasian

family study to confirm this could be made for only one of them. Therefore the possibility of Hb S- $\beta$ -thalassemia could not be entirely ruled out in the others.

The two adult patients with Hb S- $\beta$ -thalassemia were mildly affected, and the presence of hemoglobin A, S, and F is consistent with the diagnosis. The adult patients with Hb S-C and homozygous Hb C disease in Table 2 were also mildly affected.

Details on the family in which Hb S, a  $\beta$ -chain abnormality, interacted with the gene for an  $\alpha$ -chain variant, Hb G Philadelphia, have been reported.<sup>27</sup>

Two adult patients posed great diagnostic problems before we examined them. One had Hb S combined with Hb B<sub>2</sub>, a hemoglobin with abnormal delta chains, and one had Hb B<sub>2</sub> associated with  $\beta$ -thalassemia. Routine laboratory examinations on paper electrophoresis at pH 8.6 had not shown the presence of Hb B<sub>2</sub>, a small component slower than Hb A<sub>2</sub>, not detectable by paper electrophoresis. It was shown only on starch gel electrophoresis. Its presence with Hb S led to mild anemia and slight hematological changes. The patient's mother had the Hb B<sub>2</sub> trait and her father was an Hb S trait carrier. One son was an Hb B<sub>2</sub> carrier; the other son and a grandson carried the Hb S trait (Figure 1). Similar hemoglobin combinations have been described before.<sup>28,29,30,31.</sup>

The Hb B<sub>2</sub> associated with  $\beta$ -thalassemia in one man was recognizable by the presence of double



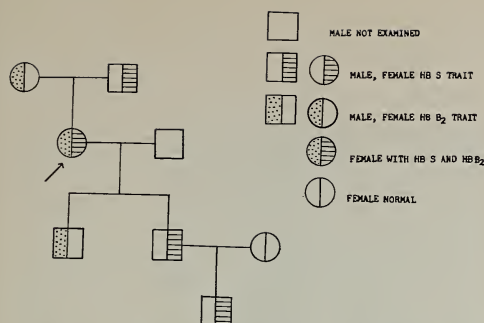


Figure 1.—Pedigree of a patient doubly heterozygous for Hb S and Hb B<sub>2</sub>.

the proportion of hemoglobins A<sub>2</sub> and B<sub>2</sub> usually seen in an Hb B<sub>2</sub> trait carrier, the sum of the two hemoglobins being the amount usually found for Hb A<sub>2</sub> in typical  $\beta$ -thalassemia. The patient had slight hematological symptoms similar to those described by Huisman et al<sup>32</sup> and Pearson and Moore<sup>31</sup> for similar combinations.

Of the seven persons with Hb H disease in four San Francisco Bay Area families, four were adults and three were children; three were unrelated Chinese, two were Filipinos, and two of Filipino-Mexican origin. The last two were children of one of the Filipinos (Figure 2) and his Mexican wife. This family was especially interesting in that the wife and a third child did not show signs of thalassemia or have any abnormal hemoglobin. Hemoglobin H is currently believed to be the result of inheritance of two  $\alpha$ -thalassemia genes, one mild and one severe.<sup>33,34</sup> The two children with Hb H disease may have received one abnormal  $\alpha$ -thalassemia gene from the father and one abnormal gene from the mother. If so, the abnormal  $\alpha$ -thalassemia gene in the mother and the third son was poorly expressed. However, one should keep in mind that the father's two abnormal genes may not have been allelic and the two sons with Hb H disease may have received both abnormal genes from the father, while the third son may have re-

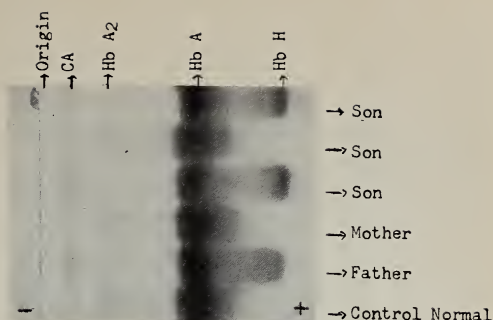


Figure 2.—Starch gel electrophoresis at pH 8.6 showing Hb H in two sons and their father while the mother and another son had normal hemoglobins. Stained with amido-black. CA = carbonic anhydrase.

ceived normal genes from both parents. Hb H disease in two successive generations is rare but occurs in areas where thalassemia is prevalent.

Table 2 does not reflect the frequency or relative incidence of hemoglobinopathies in the San Francisco area, since most cases that could be easily diagnosed by tests in a routine hematological laboratory were not referred. Nor does it reflect incidence by age, since most hemoglobinopathic conditions in children apparently were not brought to our attention. The data do show, however, the presence of a great variety of abnormalities in hemoglobin production that may lead to clinical and hematological symptoms.

### Enzymes

*Glucose-6-phosphate dehydrogenase.* Table 3 shows frequency by racial groups. None of 857 Caucasians were G-6-PD-deficient, but one 17-year-old Caucasian boy (not shown on the table) who was referred for consultation because of chronic nonspherocytic hemolytic anemia was almost completely deficient, although both parents were normal (Figure 3). This boy's leukocytes were also G-6-PD-deficient.

Specific staining for G-6-PD after electrophore-

TABLE 3.—Glucose-6-phosphate Dehydrogenase Deficiency by Race in the Healthy and Patient Populations Studied

Race	Healthy Persons				Patient				Healthy Persons and Patients			
	Male		Female		Male		Female		Male		Female	
	No.	Deficient	No.	Deficient	No.	Deficient	No.	Deficient	No.	Deficient	No.	Deficient
Caucasian	42	0	26	0	376	0	413	0	418	0	439	0
Negro	66	7 (10.6%)	71	2	137	14 (10.2%)	330	9	203	21	401	11
Filipino	116	13	27	0	8	2	3	0	124	15	30	0

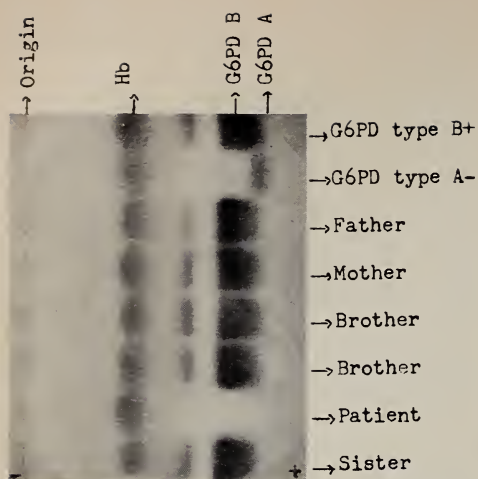


Figure 3.—Starch gel electrophoresis of erythrocyte G-6-PD at pH 8.6. Patient of Norwegian-Danish origin with chronic nonspherocytic hemolytic anemia showing severe G-6-PD deficiency. His parents and siblings were not deficient.

sis of hemolysate of blood specimens showed that the phenotype of all 768 Caucasians examined was Gd(+), B.<sup>35</sup> Of 175 male Negroes examined, 125 had the normal phenotype Gd(+), B; 29 had Gd(+), A; and 21 had Gd(—), A—. Of 333 female Negroes, 235 had the phenotype Gd(+), B; 52 had Gd(+), AB; 33 had Gd(+), A; 4 had Gd(+), B, A—; and 9 had Gd(—), A—. Of 124 male Filipinos, 103 had Gd(+), B, and 13 were deficient to such an extent that the pattern often remained invisible even after prolonged staining. Whenever the pattern could be seen, mobility was similar to that for the B type. The deficient variants from the Philippines, although having the same mobility as the B type, belong to different groups having different kinetic characteristics (Motulsky, personal communication). One man had an enzyme that migrated slightly faster than B but slower than A. All 15 Filipino women in this study had the Gd(+), B phenotype.

Although many Negroes and Filipinos in this survey had G-6-PD deficiency, none had complaints due to hemolysis. However, two Negro patients, one man and one woman, were referred for consultation because of a mild hemolytic episode leading to anemia. Both had G-6-PD deficiency of the A— type. One Filipino was referred

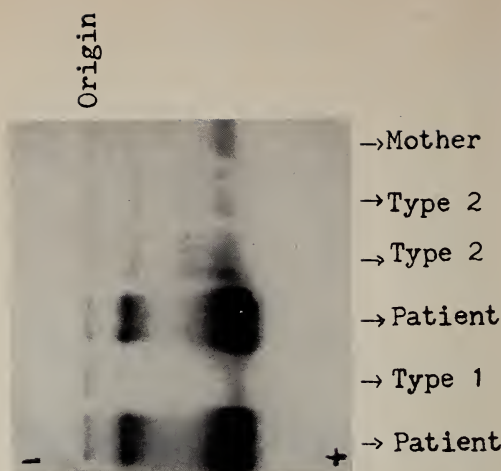


Figure 4.—Starch gel electrophoresis of serum alkaline phosphatase. Note extremely high activity in the two siblings with severe bone disease compared with the normal serum alkaline phosphatase patterns.

for special study because of rather severe hemolysis. He was G-6-PD deficient, and electrophoretic study of his hemolysate showed no visible G-6-PD activity.

**Other enzymes.** Gene frequencies for the common phosphoglucumutase types 1 and 2 in Filipinos do not differ greatly from those in Caucasians, Negroes, and Chinese reported earlier by the author,<sup>36,37</sup> but among the four groups the PGM 1 gene frequency of 0.736 in Filipinos is the lowest. While variants of carbonic anhydrase are rare, we found one (still under study) in 730 Negroes and two instances of the CA Ic variant in 140 Filipinos.<sup>38</sup> Two others have since been reported in Indonesians, one of them in San Francisco.<sup>39</sup> We found no acatalasemia in the 1,759 subjects in this study. Lactate dehydrogenase isozyme 5 was definitely increased and clearly seen on starch gel electrophoresis in 12 cases of chronic hemolytic anemia with high reticulocytosis. One Caucasian woman with chronic nonspherocytic anemia showed pyruvate kinase deficiency. Alkaline phosphatase activity was extremely high in the blood of two Filipino-Puerto Rican children, a boy and girl who were siblings with severe bone changes, probably of hereditary origin. The increase could clearly be seen on starch gel electrophoresis (Figure 4).



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## PREVENTING INFECTION AFTER SPLENECTOMY

"We recommend the following guidelines for preventing overwhelming infection in the post-splenectomy period: first to delay the operation, if possible, until the patient is older than 2 years of age (patients most at risk are those less than 2 years of age, with the majority less than 1 year of age); and second, to use penicillin prophylaxis for at least 2 years following the operation."

Do you believe that every patient should have prophylactic penicillin for 2 years following splenectomy, regardless of his age and underlying disease state?

"For the minimal risk group, including those with spherocytic hemolytic anemia or idiopathic thrombocytopenic purpura, we would 'prophylax' irrespective of the patient's age, even if the surgery were done at 7 or 8 years of age. This is especially true of idiopathic thrombocytopenic purpura."

—WILLIAM H. ZINKHAM, M.D., Baltimore  
Extracted from *Audio-Digest Surgery*, Vol. 16, No. 4, in the Audio-Digest Foundation's subscription series of tape-recorded programs.

# Rehabilitation of Paralytic Dysphonia

MORTON COOPER, PH.D., *Los Angeles*

■ *Vocal rehabilitation has been successful for patients with paralytic dysphonia. At the discretion of the laryngologist, vocal rehabilitation is used alone or in combination with intracordal injection. Except for post-surgical patients, a complete diagnostic evaluation is advisable before vocal therapy is undertaken. During vocal rehabilitation, pitch, volume, quality, breath support and the vocal image are realigned to afford an optimal and efficient voice.*

*For the 18 patients completing vocal therapy, the results were excellent in 14 and good in four. Vocal therapy was completed within six months for 11 patients; seven were treated for periods ranging from six months to a year.*

VOCAL REHABILITATION as a major means of treatment for paralytic dysphonia can be successfully carried out whether the condition is post-surgical, viral, or idiopathic in nature. The decision concerning the best approach for such patients must necessarily involve the laryngologist and the voice pathologist, with the former assuming the usual responsibility for the patient's management. Complete diagnostic evaluation is necessary in all except post-surgical cases.

In vocal therapy for abductor paralysis, if the paralyzed cord is in a position other than midline, the first step is usually strong effort to force the vocal folds to approximate. With the approximation of the vocal folds, the optimal pitch level and range are located. The optimal pitch level is that point in the total pitch range where the most efficient and easiest voice is produced with the least effort. Methods of finding the optimal pitch level have been outlined by Fairbanks,<sup>1</sup> Pronovost,<sup>2</sup> Snide-

cor,<sup>3,4</sup> and Anderson.<sup>5</sup> Determining it, Brodnitz<sup>6</sup> and Anderson<sup>7</sup> emphasize, depends largely upon a highly trained voice therapist's ear. Following determination of the optimal pitch level, this voice is developed with a correct "mask" focus—balanced oral and nasal resonance. For midline paralysis (unilateral), a moderate degree of volume is applicable for sound production. The pitch range almost invariably needs to be raised to reach the optimal pitch level, and then a new balanced tone focus is established.

Most patients cannot produce a clear easy tone in mechanical exercises or in speaking. It is best to have the patient keep his lips together and try for a tone and sound such as "um-hum," keeping the beginning syllable and the final syllable on the same pitch level. The "um-hum" must be easy and gentle and placed in the tone focus of the mask. The next step has the "um-hum" proceeding to "um-hum one, um-hum two" so that the "um-hum" and the number are matched in pitch and in tone focus. Thus, the mask focus is produced and then the oral tone is stressed, attempting to establish a carry-over from purely mechanical exercises to spontaneous interpersonal speaking.

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Submitted 15 October 1969.

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If the voice is too loud following establishment of the optimal pitch level and correct tone focus, volume should be modified. Mid-section breath support is pertinent for a healthy, comfortable voice when the proper tone focus and optimal pitch range are established. Additional therapy techniques and suggestions have been described elsewhere.<sup>7</sup>

The patient in vocal rehabilitation usually has a vocal image. A vocal image is a tone or a voice the patient either espouses or declines because it either pleases or displeases his needs, desires or aesthetic vocal posture. Essentially, the vocal image involves pitch, but it may include quality, volume and rate. The vocal image must be resolved for successful vocal rehabilitation. The vocal identity of the patient may need to be changed and a new vocal role developed.

The intracordal injection of synthetic substances in paralytic dysphonia has been discussed by Rubin,<sup>8,9,10,11</sup> Arnold,<sup>12,13,14</sup> and Luchsinger and

Arnold.<sup>15</sup> Rubin<sup>11</sup> injects Silicone® immediately to afford temporary relief. If cordal function does not return or the paralyzed cord remains in the paramedian or intermediate position after six months, he then injects Teflon®. Experience with this modality is generally favorable in experienced hands, according to Rubin. In unilateral paralysis with the cord in the median position, I have found that vocal rehabilitation alone almost always produces excellent results. If the cord is in the paramedian position, vocal rehabilitation alone may or may not be successful. Arnold<sup>14</sup> wrote:

"Intrachordal injection should not be considered before all possible attempts at vocal rehabilitation by voice therapy have been made. As is well known, many patients are capable of overcoming their vocal disability through systematic development of intralaryngeal compensation and better exploitation of the vocal-auditory feed-back mechanism...."

"For the same reason, injection should not be considered before six months have elapsed since the onset of laryngeal paralysis." And: "Afterwards, voice therapy should be resumed again for achievement of optimal functional results."

Luchsinger and Arnold<sup>15</sup> stated:

"Vocal rehabilitation through appropriate voice therapy should always be tried first. . . . Following phonosurgical intervention, voice therapy is important to achieve an optimal 'tuning' of the artificially changed vocal-cord dimensions."

Thus, intracordal injections may make the vocal folds approximate, but the laryngeal control is uncertain in some patients. Vocal rehabilitation is then required to retrain the patient in the proper use of the speaking voice, for continued vocal misuse would result in hoarseness, vocal fatigue,

TABLE 1.—Data on 41 Patients with Paralytic Dysphonia Evaluated for Rehabilitation Therapy

	No. of Patients	Evaluation Only	Entered Therapy	Inconclusive	Completed Therapy
Males	19	7	12	4	8
Females	22	11	11	1	10
Total	41	18	23	5	18
Clinic	19	10	9	4	5
Private	22	8	14	1	13
Operation as Cause of Paralysis	16	5	11	1	10
Intracordal Injections:					
Teflon®	6	1	5	1	4
Silicone®	2	1	1	..	1

TABLE 2.—Results of Treatment of Paralytic Dysphonia

	Long Term* Therapy		Short Term** Therapy		Total, Long Term and Short Term Therapy	
	Excellent†	Good‡	Excellent	Good	Excellent	Good
Males	3	1	3	1	6	2
Females	3	..	5	2	8	2
Total	6	1	8	3	14	4
Clinic	2	..	1	2	3	2
Private	4	1	7	1	11	2
Operation as Cause of Paralysis	2	1	5	2	7	3
Intracordal Injections:						
Teflon®	..	..	2	2	2	2
Silicone®	..	1	..	..	..	1

\*Over six months.

\*\*Six months or less

†Excellent is defined as a clear, smooth, easily projected voice which is used almost all of the time.

‡Good is defined as a clear, smooth, easily projected voice which is used most of the time.



laryngeal and pharyngeal pain, and other symptoms.

### Experience with Treatment

In a period of five years, 41 patients with vocal fold paralysis were treated. The age range was 19 to 71 years, and there were 19 males and 22 females. The frequency of meetings depended upon time, circumstances, and the needs of the patient.

The essential complaints in all cases were vocal fatigue and poor vocal projection. Hoarseness was one of the cardinal symptoms of the persistently dysphonic patient.

Sixteen of the patients were referred after subtotal or total thyroidectomy, some of them within a few weeks and some many months after operation.

Data on all patients evaluated and the results obtained in those treated are given in Tables 1 and 2.

From the tables it may be concluded that:

- For the 18 patients completing therapy the results were excellent in 14 and good in four.
- Males and private patients were more likely to enter therapy than were females and clinic patients.
- Females and private patients were more likely to complete therapy than were males and clinic patients.
- Therapy lasted less than six months (short-

term therapy) for 11 patients; only seven patients were seen for more than six months (long-term therapy).

- Six of seven patients in long-term therapy had excellent results.
- Eight of 11 patients in short-term therapy had excellent results; the other three had good results.

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### ALL THAT SUPPURATES IS NOT INFECTION

"I always worry about gross pus in the urine because you can get into trouble if you don't remember that pus is a sign of inflammation, but not necessarily a sign of infection. It could be cancer of the bladder. So the fact that you see pus in the urine doesn't say that it is infection; it means that there's some inflammation. . . . The other thing about pus is that there may be so much that you can't see any bacteria at all. . . . So if you see a tremendous amount of pus, you have to remember that it will obscure the bacteria. You always must remember that it can be due to trauma or it could be due to tumor. Just don't make a diagnosis of infection."

—CALVIN M. KUNIN, M.D., Charlottesville  
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# Percutaneous Cordotomy

## A Simplified Approach to the Management of Intractable Pain

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■ *Cordotomy for palliation of intractable pain was simplified by the use of a stereotactic percutaneous technique. The procedure is performed at the high cervical level and has been found to give good results for pain in the upper as well as the lower extremity and the trunk. Respiratory complications are the major hazard, but they may be reduced by careful selection and evaluation of patients.*

THE INTRODUCTION of percutaneous cordotomy by Mullan<sup>1</sup> in 1963, and its modification by Rosomoff<sup>2</sup> in 1965, gave neurosurgery a useful new tool for the management of intractable pain. This modification of the classical spinothalamic tractotomy, as first performed by Spiller and Martin<sup>3</sup> and by Foerster and Gagel,<sup>4</sup> has greatly simplified high cervical cordotomy. It has minimized operative morbidity to such an extent that neurosurgeons may operate on many pain-ridden patients who would heretofore have been considered excessive surgical risks and thus have been denied the benefit of pain relief.

### Technique

We employ the technique used by Rosomoff<sup>2</sup> but have introduced some modifications. The most significant of these is a pin-fixation head stabilization device, which we consider essential, for with-

out it the patient may move about during the procedure and seriously injure the spinal cord with the fixed needle electrode.

The operation is carried out under local anesthesia with the patient lightly premedicated and sufficiently responsive to be cooperative during sensory testing later in the procedure. The patient is placed in the supine position and the head is secured in the pin-fixation frame (Figure 1). A preliminary film, taken with a grid suspended from the patient's cheek with adhesive tape, helps in locating the C1-C2 interspace (Figure 2). A No. 18 or thin-walled No. 19 spinal needle is advanced into the lateral aspect of the neck until the subarachnoid space is entered at this level. Air is injected to outline the anterior border of the spinal cord (Figure 3). Fine adjustments of needle position are made under radiographic control with either Polaroid® film or a portable image intensifier. A coated fine wire electrode\* is introduced into the needle (Figure 4) and a thermal coagulative lesion is made† (Figure 5). Pain perception is tested with a pin, the lesion is enlarged or the position of the

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\*Manufactured by Micron Instruments, Inc., 1519 Pontius Ave., Los Angeles, Ca. 90025.

†The Coagrader radiofrequency generator, manufactured by N. V. Vitatron, Valeriusstraat 26, Amsterdam, The Netherlands, has been used.



Figure 1.—Cervical radiofrequency cordotomy showing how patient's head is secured in pin-fixation frame and needle in position for subarachnoid puncture (representational model).

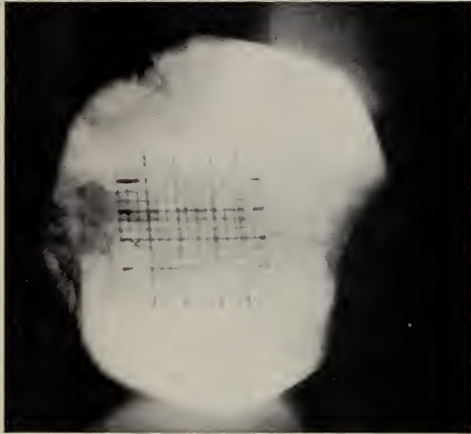


Figure 2.—Polaroid® scout film of upper cervical spine with metallic grid in position. The X marks the point for optimal placement of the needle in the C1-C2 interspace.

needle electrode is adjusted, and the lesion is duplicated until the desired analgesia is obtained.

If patients become restless during the procedure we have found intravenous Valium,®\* administered in small amounts, to be useful. The needle is withdrawn at the conclusion of the procedure, and small adhesive bandages are applied. The patient is permitted to get up on the day following the procedure and many patients can be discharged from the hospital on the third postoperative day.

\*Brand of diazepam (Roche Laboratories).



Figure 3.—Upper cervical spine with air outlining anterior aspect of the spinal cord in lateral projection. In the upper portion of the C1-C2 interspace a horizontal air-fluid level is present.



Figure 4.—Anteroposterior projection of upper cervical spine (open-mouth view) showing relationship of needle to odontoid process. The electrode can be seen to project beyond the needle tip.

Patients tolerate the procedure without difficulty and at most complain of mild headache.

Strictly unilateral pain is treated by lesions placed on the opposite side of the spinal cord. Midline pain, except when it is predominantly

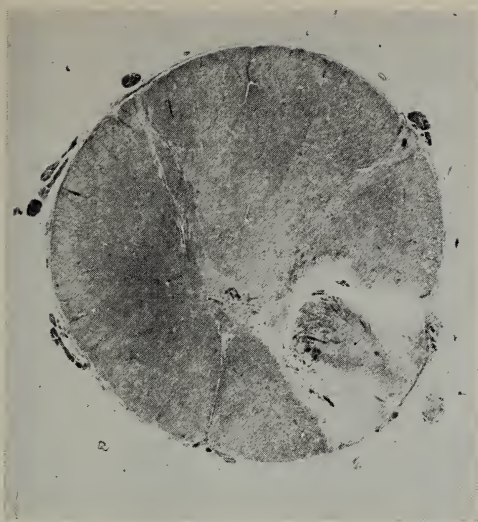


Figure 5.—Autopsy specimen of spinal cord following unilateral anterolateral cordotomy. The patient had excellent relief of pain but had a nonfunctioning lung on the side of thoracic pain. Dyspnea developed 24 hours after operation and the patient died on the seventh postoperative day. Never was any extremity weakness manifested.

lateralized to one side, often requires bilateral cordotomy. Bilateral pain requires bilateral pain relieving procedures.

Anticipated side effects of the procedure, aside from mild headache and neck discomfort lasting one or two days, include a Horner's syndrome on the side of the operative procedure. The patients should be warned that transient weakness may develop on the side on which the lesion is made, that is, on the side opposite the pain, and cautioned regarding the expected decrease in skin temperature and loss of pain sensation which may involve the entire half of the body below the neck. Sense of touch and proprioception remain intact. It is not uncommon for the level of anesthesia to ascend within the first 24 hours after cordotomy, and no guarantee can be made that the upper extremity will be spared when a lesion is placed for analgesia of the lower extremity or trunk. The physician should recognize that an effective cordotomy for unilateral pain may unmask pain on the opposite side, which has been previously asymptomatic, or that pain may be referred to the opposite side postoperatively.<sup>5</sup> This may occur even though the physician specifically disclaimed bilateral pain before cordotomy.

TABLE 1.—Causes of Pain in 47 Patients Who Underwent Percutaneous Cordotomy

Malignant disease, primary site	
lung	15
genitourinary tract	10
colon	8
other	8
Total	41
Benign disease	
postherpetic neuralgia	2
chronic lumbar root pain (postoperative)	2
pain secondary to flank incision	1
osteoarthritis	1
Total	6

TABLE 2.—Effectiveness of Percutaneous Cordotomy in 47 Patients

	Patients with Malignant Tumors	Patients with Benign Disease	Totals	Percent
Excellent	23	3	26	55
Good	4	..	4	8
Fair	11	1	12	26
Failure	3	2	5	11

The present report covers our experience with 60 percutaneous cordotomy operations performed on 47 patients by members of the Division of Neurosurgery at the UCLA Hospital and the affiliated service at the Wadsworth Veterans Hospital during the years 1965 to 1969. Staged bilateral procedures were carried out in six patients and six patients required more than one procedure on the same side to produce an effective lesion. All the patients in this series had intractable pain due to organic disease requiring large doses of narcotics at frequent intervals. The causes of the pain in these patients are listed in Table 1.

## Results

The success of the procedure is evaluated by the degree of pain relief. Many patients, however, develop drug dependency before cordotomy is performed, and narcotics cannot always be withdrawn immediately after the pain-relieving procedure is carried out, even though the procedure is successful. A sensory level, well above the site of previous pain, is usually maintained when pain relief is achieved. No instance of paradoxical sensory loss ipsilateral to the spinal cord lesion was encountered.

Postoperative results were considered excellent when patients were free of pain, good when they had some pain but were comfortable, and fair when



there was only slight improvement from the pre-operative pain (Table 2).

Of the 41 patients with malignant disease, five died in the postoperative period and the remaining patients survived from one to fourteen months after cordotomy. Fifty per cent of patients with malignant tumors were dead six months after cordotomy and 95 percent had died of the disease one year after the procedure. All patients who underwent cordotomy for pain due to benign conditions are currently alive.

The follow-up period for the entire group of patients extends from one month to 30 months. Three of five patients who had little or no relief of pain had had previous unsuccessful operations for pain relief as long as two years and as recently as two months before the attempted percutaneous cordotomy. These included a frontal lobotomy, medullary tractotomy and an open cordotomy.

### Complications

The most serious complication encountered was that of respiratory embarrassment, accounting for the five postoperative deaths. Two patients are presumed to have developed sleep apnea and died at home. Three patients died seven, ten, and twenty-two days after cordotomy, but death in those cases was not clearly due to sleep apnea. Three of the deaths occurred in patients who underwent staged bilateral procedures seven days, one month and ten months apart. The remaining two deaths occurred six and eleven days after unilateral cordotomy in patients whose remaining functioning lung was on the side on which the spinal cord lesion was placed.

Nonfatal transient cardiovascular-respiratory problems were encountered in another two patients, both of whom had undergone cordotomy for pain on the side of a nonfunctioning or absent lung.

Transient motor weakness ipsilateral to the side of the spinal cord lesion was encountered in 11 patients (23 percent), but it usually improved within seven to ten days with the help of physiotherapy.

In three patients (6 percent), all of whom had had unilateral procedures, transient urinary retention developed, requiring catheterization. In each instance the catheter could be removed after a few days.

In one patient we were unable to outline the anterior border of the spinal cord by injection of air, although good flow of cerebrospinal fluid was obtained. In this patient evidence of cervical spinal

cord compression developed some weeks after the attempted cordotomy, and a carpet of subdural metastatic tumor was found at laminectomy.

### Discussion

#### *Pain due to malignant tumor*

In the present series the effectiveness of percutaneous cordotomy proved to be of the same order as reported by other observers.<sup>1,2,6</sup> The general experience, as well as our own, has been that these results are somewhat better than those reported following classical high cervical cordotomy by the open technique.<sup>7</sup> In 11 of 13 patients with Pancoast's syndrome or upper extremity pain percutaneous cordotomy at the C1-C2 level produced effective pain relief up to the time of death, two to five months later. Upper extremity pain relief is difficult to achieve with high cordotomy by the open technique, usually performed at the C2 level. Sixty-three per cent of our patients obtained good to excellent relief of pain. An additional 26 percent of our patients had fair relief of pain. Our operative mortality of five patients (11 percent) compared favorably with that reported for the open high cervical cordotomy<sup>7</sup> and is being further reduced by better patient selection. The operation was ineffective in five patients (11 percent).

The major advantage of the percutaneous technique of cordotomy lies in the fact that patients with malignant tumors, often in a poor nutritional state, are not subjected to a major surgical procedure under general anesthesia. The difficulties that may be encountered with wound healing in the cervical or thoracic regions of patients with advanced cancer can be substantial, whereas the needle tract heals over without any difficulty. In many cases cordotomy by laminectomy was carried out under local anesthesia, but this is not always possible and is a taxing procedure for both patient and surgeon. The percutaneous procedure is ideally suited to local anesthesia. These factors undoubtedly account for the lower operative mortality following the percutaneous procedure.

Thus the percutaneous electrode technique has extended the applicability of cordotomy to a large number of patients who would previously have been denied adequate pain relief. Only patients who are clearly near death are not considered candidates for this procedure.

Our experience with percutaneous cordotomy performed for the relief of pain in patients with

malignant tumors has also provided us with important guides for the selection of patients. The three deaths in the patients who underwent staged bilateral cordotomy were all due to respiratory problems. Fatal respiratory complications following bilateral high cervical cordotomy have been encountered by other surgeons even when the two procedures are staged.<sup>5,7,9-11</sup> The pathophysiology of these respiratory problems is not entirely understood and does not appear to be identical in every patient. Sleep apnea or "Ondine's curse" has been reported as the cause of death in patients with bilateral high cervical cordotomy by Belmusto,<sup>9</sup> Tenicela et al,<sup>10</sup> and Mullan.<sup>11</sup> Sleep apnea results from interference with the involuntary respiratory drive—impulses which are transmitted from the medulla via the spinal cord to the diaphragm and intercostal muscles. This mechanism may explain the death of two of our patients. The respiratory problems leading to death in three other patients were not as well defined but may have been due to a similar mechanism.

Unilateral diaphragmatic paralysis may occur due to injury to descending fibers terminating about the anterior horn cells of phrenic nerve axons. Two patients underwent fluoroscopy before the second stage of staged bilateral cordotomy (one month and ten months after the first procedure) and their diaphragms were observed to move well, yet they died 22 and 10 days, respectively, after the second procedure. Nathan<sup>12</sup> demonstrated recovery of function of the paralyzed hemidiaphragm in man several weeks after unilateral cordotomy. He discussed the various mechanisms by which reinnervation might take place, including the possibility that contralateral spinal cord pathways might take over the function of the destroyed ipsilateral afferent connections to the diaphragm and intercostal muscles. Thus, fluoroscopic examination of the chest shortly after a high cervical anterolateral cordotomy was performed, might demonstrate paralysis of the ipsilateral diaphragm. Fluoroscopy performed several weeks later, however, would not necessarily show any evidence of residual diaphragmatic palsy. When the opposite anterolateral quadrant cordotomy is then undertaken, the innervation to the entire diaphragm would be jeopardized at once, leading to respiratory embarrassment.

Patients who have severely impaired pulmonary function are subject to similar risks. This category includes cancer patients with diffuse pulmonary

disease, such as severe emphysema. More common are those patients with cancer of the lung who have an extensive pleural effusion or consolidation or who have pain on the side of a previous pneumonectomy. The spinothalamic tract lesion must be placed on the side of the spinal cord opposite the pain, and thus in proximity to the spinal cord pathways which innervate the diaphragm and intercostal muscles ventilating the intact lung. Two such patients died in the early postoperative period and transient dyspnea and hypotension developed in two others. It is important to point out, however, that some patients with a similar picture of pain and poor pulmonary function tolerate unilateral cordotomy without complications.

We now routinely study pulmonary function in all patients before cordotomy because of the seriousness of such respiratory complications. Avoidance of bilateral procedures pending modification of the technique would seem advisable. Similarly, we are not enthusiastic in recommending this procedure for patients with intractable pain who have poor pulmonary function on the same side as their pain. Low percutaneous cervical cordotomy as proposed by Lin et al,<sup>13</sup> although a more cumbersome procedure, appears to be useful in patients with problems of this type and may be combined with high cervical cordotomy when necessary.

#### *Pain due to benign disease*

White<sup>7</sup> pointed out that cordotomy is often an unsatisfactory procedure for the relief of pain that is due to benign but nonetheless organic disease. Pain begins to recur in some patients after six to twelve months.

In our limited experience, the results of percutaneous cordotomy in patients with benign disease were not as good as in patients with malignant tumors (Table 2). The character of the pain in these patients is often more diffuse and difficult to define and the pain is frequently of long standing. The relief of pain in one patient with postherpetic neuralgia for 19 months and in another patient with lumbar root pain for 20 months, however, is significant. It is of interest that three patients in this group had undergone previous unsuccessful neurosurgical procedures for the relief of pain. This suggests that an incomplete lesion in the lemniscal pathways of the spinal cord or brainstem might encourage pain stimuli to travel via extra-lemniscal routes, which would not be destroyed by anterolateral cordotomy.



We have been especially careful in the selection of candidates for cordotomy among those patients whose pain is due to benign conditions. We insist that they undergo a diagnostic subarachnoid block as well as sympathetic blocks with an appropriate local anesthetic whenever applicable. In one patient who had had a thigh amputation, chronic stump pain persisted in spite of effective total spinal anesthesia to a low thoracic level, which suggested a central pain mechanism.

Pulmonary function studies are also carried out in this group of patients if they seem suitable candidates for percutaneous cordotomy.

## General Aspects

Percutaneous radiofrequency cordotomy is not accompanied by severe discomfort and is not a prolonged operation. The procedure may be repeated if the first operation fails to alleviate pain. In the present series it was repeated in six patients, in four of whom pain was due to a tumor which was malignant, and two in which the disease was benign. It should be pointed out, however, that in only two of the four patients with cancer, and in neither of those with benign disease did the second attempt bring about the desired relief.

We have observed occasionally that some pain relief is obtained without a demonstrable sensory level of anesthesia. Mullan<sup>1</sup> described the same phenomenon with radioactive strontium lesions. We observed it in one patient who had good degree of pain relief. Occasionally a sensory loss was obtained at the time of operation but pain was not relieved until the day following the procedure. The reason for this is not clear.

Percutaneous radiofrequency cordotomy is a

valuable palliative procedure for patients with intractable pain due to malignant tumor. Because the rate of morbidity and mortality in properly selected patients is low, it is desirable that cordotomy be done before the patient reaches a near-terminal state so that he may benefit from pain relief for the maximum period. Cordotomy is of more limited usefulness in patients with organic pain due to benign disease.

**Acknowledgement** — The authors gratefully acknowledge the technical assistance of Mr. Everett M. Carr, electronic technician, who participated in all of the procedures. Richard E. Balch, M.D., contributed to the design of the head holder and stereotactic manipulator currently in use.

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# CASE REPORTS

## Surgical Treatment of Traumatic Rupture of the Thoracic Aorta and Diaphragm

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TRAUMATIC LACERATION of the thoracic aorta secondary to blunt trauma of the chest is occurring with increasing frequency. Deceleration injury, such as that encountered in auto accidents at high speed, seems to be the major factor. Fewer than 15 percent of patients with this injury survive to reach a hospital.<sup>1</sup> Early diagnosis of the problem is mandatory and nonoperative management is uniformly associated with a high mortality. Since the first successful repair in 1959<sup>2</sup> there have been approximately 30 surgical cases reported.<sup>3</sup> The following is the first report of successful repair of traumatic ruptures of the thoracic aorta and left hemidiaphragm.

### Report of a Case

A 21-year-old man was admitted to the Santa Clara Valley Medical Center 25 October 1968 on transfer from another hospital two hours after injury in an automobile crash at high speed. At the other hospital an x-ray film of the chest showed a widened mediastinum. On admission the patient

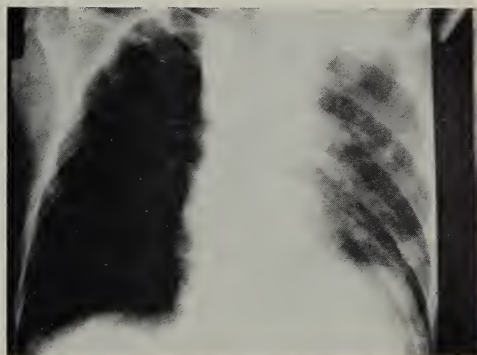


Figure 1.—Preoperative x-ray film showing widened mediastinum and elevation left of hemidiaphragm.

was awake and alert. The extremities were pale and cool. There were superficial lacerations of the face and scalp and he complained of pain in the back and left chest. The blood pressure in the left arm was 136/72 mm of mercury and the pulse was 120 and regular. The peripheral pulses were palpable although those in the lower extremities were weak. Auscultation of the chest disclosed normal breath sounds on the right and decidedly decreased breath sounds on the left. A loud systolic bruit with radiation to the back was audible just below the left mid-clavicle. The left upper abdominal quadrant was tender to palpation but rebound tenderness was absent. Bowel sounds were normal. Results of neurological examination were entirely within normal limits. A radiograph disclosed a wide mediastinum, multiple rib fractures on the left and an elevation of the left hemidiaphragm (Figure 1). Urinalysis showed 1+ protein, 4+ glucose with 20 to 30 erythrocytes per high-power field. The hematocrit was 37 percent and leukocytes numbered 27,000 per cu mm. Serum electrolytes were within normal limits. Approximately an hour after admission, an emergency retrograde aortogram using a percutaneous femoral approach was performed. This study disclosed an intraluminal filling defect and traumatic aneurysm in the descending aorta just

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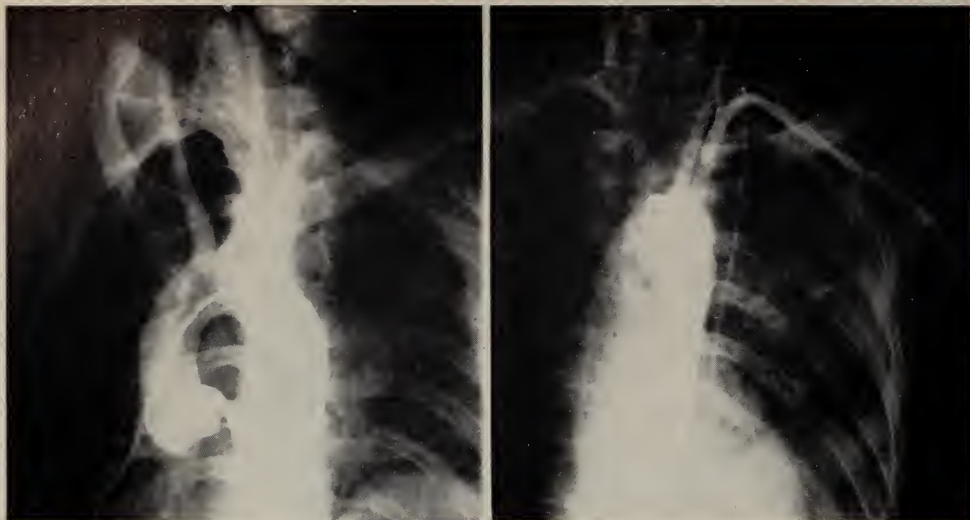


Figure 2.—*Left*, aortogram showing a nearly vertical thin radiolucent line within a collection of contrast medium just distal to the left subclavian artery. This intraluminal filling defect represents an intimal tear (left-posterior-oblique projection). *Right*, view from front showing traumatic aneurysm in the descending aorta.

below the left subclavian artery (Figure 2). Vital signs remained stable throughout the procedure.

The patient was then transferred to the operating room where left femoral vein to femoral artery by-pass was effected while simultaneous left thoracotomy was being performed. An oblique 3 cm tear of the aorta was found just distal to the left subclavian artery. The traumatized section of aorta was excised and replaced with a dacron tube graft. The partial by-pass time was 44 minutes. A tear in the left hemidiaphragm extending from the xiphoid process to the aortic hiatus was closed with interrupted nonabsorbable sutures reinforced with a running suture of 0 chromic catgut. Except for transient weakness in the left lower extremity, the postoperative course was uneventful. The tubes were removed from the chest on the third postoperative day and the patient was discharged on the 13th postoperative day. At last report, 6 months after operation, he was asymptomatic and the blood pressure was within normal limits.

## Discussion

With the increased number of high speed automobile accidents, rupture of the aorta as a result of abrupt deceleration is increasing. Greendyke<sup>4</sup> reported that one of every six persons who died as a result of an automobile accident in Monroe

County, New York, during the years 1961 through 1965 had aortal rupture. This injury occurs in all age groups but is most common in young men.<sup>5</sup> Approximately 80 percent of all traumatic ruptures occur at the level of the ligamentum arteriosum.<sup>6</sup> In contrast to the old theory of a relative fixation of the aortic arch with a mobile descending aorta, recent evidence suggests that the descending aorta is anchored by the adjacent soft tissue, intercostal vessels and pleural reflections while the arch is quite mobile.<sup>7</sup> At the level of the ligamentum arteriosum the aorta is bound firmly to the prevertebral fascia by dense fibrous connective tissue.

The physical findings in patients with disruption of the thoracic aorta may be misleading, for there may be little or no external evidence of chest injury. When there is a history of deceleration trauma associated with widening of the mediastinum on an x-ray film, aortography is indicated. If a tear is demonstrated, surgical repair should be done immediately. Successful treatment is dependent upon early diagnosis. The primary obstacle to success is failure to recognize the problem.

With reference to traumatic rupture of the diaphragm, Ambroise Paré described the characteristic signs of this injury in 1579 as severe pain and disturbance of mechanical respiration. The diagnosis is often delayed because the injury may be

overshadowed by the pain of abdominal visceral lacerations or rupture, and chest wall trauma. This injury is also increasing in frequency and automobile accidents head the list of causative factors.<sup>8,9</sup>

## Summary

A case is reported in which rupture of the thoracic aorta in a man injured in an automobile crash was successfully carried out.

Traumatic rupture of the thoracic aorta and diaphragm is more common than appreciated. Aortography is essential when there is a history of chest trauma and widening of the mediastinum is seen on x-ray examination. A high index of suspicion and emergency operative intervention, using partial cardiopulmonary by-pass, may raise the low salvage rate of those patients who live long

enough to reach a hospital. In addition, thorough exploration of the chest at the time of operation may occasionally disclose a diaphragmatic laceration previously unappreciated.

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## LIGHT THAT BLESSES AND BLURS

"Light is a very interesting commodity. As we grow older, light becomes a two-edged sword that works for us and works against us. Because of the increased sclerosis within the media of the eye, there is a great deal more internal scatter. So we get a lot of glare if the light comes into the eye; but at the same time, we need more light on the material that we are reading. So a properly directed light is a very great help.

"I'm sure that as ophthalmologists you've all run into this experience: you prescribe reading glasses for a patient and record that he is able to read Jaeger 1; and yet the person calls up and says that he can't see with his new glasses. You're only human so you call him back to the office and with the very same glasses, he reads Jaeger 1 and says, 'How come I can read it here, but I can't read it at home?' It's largely because most of us use some form of a gooseneck lamp over our chairs; and in effect what we're getting is a concentration of light on the target, and the shade is preventing a good deal of the backlash of the light into the eye. So showing the person how to use a light is very helpful.

"This is particularly true in people who have incipient cataracts. The blur that goes with incipient cataracts is very much like the spots of dirt on the windshield of your car. The sun hits your windshield a certain way and the windshield is perfectly clean; if it hits another way, you have trouble seeing. If a person is aware of how to work his lights, he can avoid this sort of thing."

—ALBERT E. SLOANE, M.D. Boston

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## XXXY Chromosomal Abnormality in a Child

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IT IS ESTIMATED that a chromosomal abnormality occurs in approximately one of every one to two hundred live births.<sup>4,5,6</sup> About three-fourths of these abnormalities involve the sex chromosomes. The affected children may present problems of physical development and mental retardation. Early recognition and diagnosis offers the opportunity to give genetic counselling regarding future pregnancies and to plan for special training which will permit these children to reach their full potential. The following is a case report of a boy three years and nine months of age with XXXY sex chromosomal abnormality. This is believed to be the youngest age at which this anomaly has been reported.

### Report of a Case

The propositus is a three year, nine month old male of Dutch-Indonesian parentage. He was born at nine months of gestation to a para 0, gravida 1 mother 25 years of age. The prenatal period was not complicated by bleeding, infection, x-ray exposure, drugs, or systemic disease. The delivery was normal and the baby, who weighed 6 pounds 5 ounces, cried spontaneously. No significant physical findings were noted at the time of birth except for a bilateral forefoot adduction. External genitalia were considered normal.

The development of the child included the following milestones: head-holding a 5¼ months, turning over at 6¾ months, crawling at eight

months but with poor use of legs, sitting without support at 10 months, first tooth eruption at one year, walking alone at two years with a waddling gait and tendency to walk on tiptoes and frequent falling, and bowel and toilet training at 3½ years. Speech development included first words at 18 months (mama), and two to three word sentences and naming a few colors at 3½ years. The growth pattern revealed the child to be consistently small in weight and stature. At one year he weighed 16 pounds (below the third percentile) and was 29¾ inches tall (fiftieth percentile). At 3½ years he weighed 32 pounds (fiftieth percentile) and was 38¾ inches tall (twenty-fifth percentile).

The family history was not remarkable. Siblings include normal identical twin boys one year of age. There was no family history of congenital defects, chromosomal abnormalities, consanguinity, infertility or mental retardation.

The patient's history of childhood illnesses was unremarkable except for left esotropia with decreased abduction of the eye at six months of age, persistent vomiting at 23 months of age (with normal gastrointestinal and thoracic x-ray studies) which subsided spontaneously, orthopedic consultation for the forefoot adduction, and three days in hospital at 3½ years for bronchitis.

Physical examination at 3½ years revealed the following pertinent findings: The child was a thin, friendly, responsive and cooperative boy with peculiar facies due to eye-wide medial epicanthal folds and prominent lateral epicanthal folds. No esotropia was present. The mouth and teeth were normal and without a high arched plate. Heart, lungs and thoracic cage revealed no abnormalities. Testicles were palpable bilaterally and were judged to be of normal size. The penis was small and circumcised. The elbow joints were held in a position of cubital varus, with limited supination, and crepitus could be felt on pronation (Figure 1). The hands revealed no simian crease but showed incurving of the fifth fingers bilaterally. The hips were hyperextensible. The feet had a mild bilateral varus. Neurological examination was negative except for symmetrically hypoactive deep tendon reflexes. Cranial nerves were normal. Psychological testing revealed an I.Q. of 60.

Recent laboratory findings included normal blood cell count and protein-bound iodine of 5.5 mcg per 100 ml. X-ray films of the elbow joints showed radial-ulnar synostosis (Figure 2). A chromosomal preparation of peripheral blood leu-

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Figure 1.—Child at age of 3¾ years with elbow joints held in position of cubital varus.

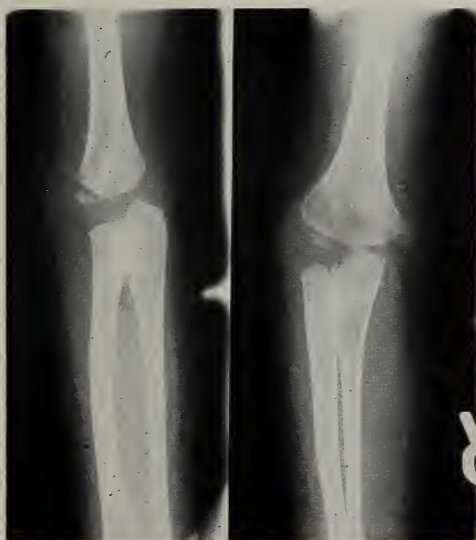


Figure 2.—X-ray film of elbows showing radial-ulnar synostosis.

kocytes revealed an XXXY sex chromosomal abnormality. The autosomal chromosomes were normal in distribution and morphologically (Figure 3). Buccal smears revealed two Barr bodies in most cells. On study of polymorphonuclear leukocytes, female "drumsticks" were noted in 9 percent of the cells.

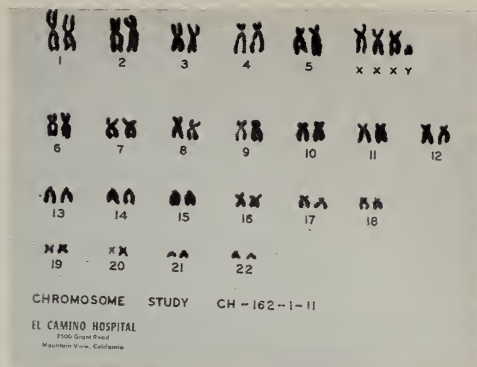


Figure 3.—Chromosomal karyotype with an XXXY chromosomal abnormality and normal autosomal chromosomes.

## Discussion

The XXXY sex chromosomal abnormality is generally regarded as a variant of Klinefelter's syndrome (XXY). As a general rule, the degree of physical abnormalities and mental retardation increases as the number of X-chromosomes increases. The patient in the present case follows this pattern. The physical findings in the XXXY cases are more pronounced than the infantile sexual development and borderline low mentality of the Klinefelter's syndrome but not as great as the gross physical abnormalities and severe mental retardation of the XXXXY chromosomal abnormality. The age of diagnosis is also directly related to the severity of the abnormalities. Most cases of true Klinefelter's syndrome are not diagnosed until puberty, when the lack of secondary sex characteristics becomes obvious. This is true also of previously reported cases of the XXXY variant, the age at diagnosis having been reported at from 14 to 22 years.<sup>1,2,3</sup> All the patients have had significant degrees of mental retardation. The patient in the present case is the youngest yet reported with the XXXY abnormality.

The origin of the abnormality appears to be a double nondisjunction of the X chromosome occurring in the first and second meiotic divisions. While it is possible that the defect may occur in either the ovum or sperm, most of the evidence supports maternal origin. Since it is the result of a sporadic nondisjunction, it is not hereditary and the parents can be reasonably reassured that future pregnancies are not likely to result in a similarly abnormal child.

The occurrence of chromosomal abnormalities is not as infrequent as was previously believed. It is essential that the diagnosis be made at as early an age as possible, the better to counsel the parents and prepare for the future problems of the child. The major features which should alert the clinician to the possibility of a chromosomal abnormality include congenital defects, especially those involving the heart, musculoskeletal system, face, palate and ears; abnormalities of the external genitalia; mental retardation; and lack of motor development. Lack of development of secondary sex characteristics and primary amenorrhea may be present in older patients.

The diagnosis of specific chromosomal abnormalities can be made with certainty only by chromosomal analysis. Peripheral blood leukocytes are easily obtainable for chromosomal cultures and are entirely satisfactory for most problems. Chromosomal analysis is now readily available at most major medical centers, at many of the larger hospitals and at commercial laboratories. The examination of buccal smears for Barr bodies is a good screening procedure for sex chromosomal abnormalities involving an increase in the number of x

chromosomes in the phenotypical male or a decrease in the number of x chromosomes in the phenotypical female (Turner's syndrome). Polymorphonuclear leukocytic "drumsticks" are often helpful but much less reliable and more difficult to interpret than the buccal smears.

## Summary

A case report of a 3¾ year old boy with an XXXY chromosomal abnormality is presented. The major clinical features consisted of delayed physical development, moderate mental retardation, abnormal facies and radial-ulnar synostosis.

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## THE EMERGENCY OF TAMPONADE

"A cardiac injury requires no treatment in the emergency room if there's no evidence of tamponade or continuing hemorrhage. However, patients are monitored quite closely for venous pressure in the intensive care unit right next to the operating room. If they do show evidence of tamponade, pericardiocentesis is the primary method of management. If the patient does not respond immediately or if tamponade recurs, immediate thoracotomy is performed without letting the patient arrest. If arrest should occur by any method of treatment, at any time, thoracotomy is immediately performed, whether on the ward, in the operating room, in the emergency room, or in the intensive care unit."

—ARTHUR C. BEALL, JR., M.D., Houston

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# Diseases of the Esophagus

## Present Concepts

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IN THE PAST TWO DECADES, much information has been accumulated about the physiologic, pathologic and anatomic manifestations of various esophageal diseases. The radiologist plays an important role in evaluating these disorders and, in most instances, roentgenographic examination in conjunction with clinical history permits accurate diagnosis. In this report a review of normal esophageal anatomy and function is followed by an analysis of several selected disorders affecting the esophagus and their roentgenographic features.

### Anatomy

The esophagus is a muscular tube, 20 to 24 cm in length, lined predominantly by stratified squamous epithelium.

The junction of the pharynx and esophagus is demarcated by the cricopharyngeal muscle which measures about 1 cm in vertical length. This muscle, at the same level as the cricoid cartilage, is the most proximal esophageal muscle component. When the pharynx and esophagus contain barium, this muscle produces a ring-like narrowing of the barium column that demarcates the pharyngo-esophageal junction. The remaining esophageal musculature begins at the lowermost border of the cricoid cartilage and interdigitates with the cricopharyngeus. Although individual variation is pronounced, striated muscle predominates the proximal one-third and smooth muscle the distal two-thirds of the esophagus.

An upper esophageal sphincter 1 to 3 cm long exists at the proximal esophagus. This sphincter is composed of the cricopharyngeus muscle and the highest circular muscles of the esophagus.

Because many names have been used to describe the various anatomic landmarks of the lower esophagus, much confusion exists about the classification and nomenclature of structures in this area. Terms used in this discussion to denote these structures, as well as synonyms frequently used, are listed in Figure 1.

A sphincteric segment 1 to 4 cm long exists at the distal esophagus. It joins the stomach at the cardia. This sphincter is located partially in the thorax, partially in the diaphragmatic esophageal hiatus and partially in the abdomen. It is joined to the diaphragm by a tough, fibroelastic membrane, the phreno-esophageal membrane. The term *vestibule*, meaning an entrance hall (to the stomach), has been used to describe this region. Much confusion persists about this sphincter because it has many synonyms (Figure 1). We prefer to characterize this area as either the vestibule or lower esophageal sphincter.

An additional short contractile area, the inferior esophageal sphincter, makes up the proximal-most margin of the vestibule. Considerable confusion also exists about this nomenclature, for some authors refer to the entire vestibule or lower esophageal sphincter as the inferior esophageal sphincter (Figures 1 and 2).

Mucosa in the closed vestibule is thrown into longitudinal folds. Barium caught between these folds produces 2 to 4 smooth, vertical, linear

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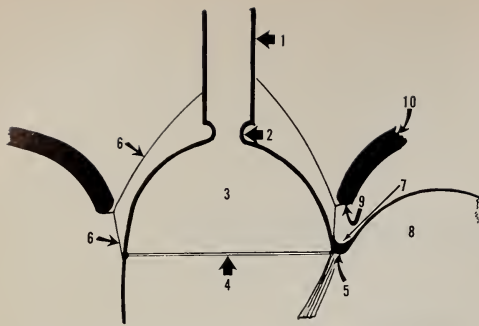


Figure 1.—Simplified diagrammatic representation of lower esophageal anatomy. Terms used in this report are in *italics* below. Synonyms frequently used for each area follow, with the name of the author (if known) responsible for introducing or popularizing each term.

1. *Lower Esophagus*  
supra ampullary esophagus (Botha, 1962)  
tubular esophagus (Wolf, 1967)
2. *Inferior Esophageal Sphincter* (Lerche, 1950)  
constriction caused by hiatus (Luschka, 1857)  
narrowing of Laimer (1883)  
sphincter-like inferior esophageal constriction (Strecker, 1905)  
constrictor cardia (Gould and Barnhard, 1957)  
sub-ampullary constriction of Hacker (Turano, 1959)  
Ring A (Wolf, 1967)  
tubulo-vestibular sphincter (Wolf, 1967)
3. *Vestibule* (Lerche, 1950) or *Lower Esophageal Sphincter*  
cardia (Sommering, 1796)  
cardiac antrum (Arnold, 1838)  
esophageal ampulla (Barclay, 1915)  
epicardia (Ackerlund, 1929)  
cardiac sphincter (Abel, 1929)  
phrenic ampulla (Templeton, 1944)  
the term "phrenic ampulla" was first suggested by Waterson (1905) to describe hiatal hernia and has been used indiscriminately by radiologists for many years  
epiphrenic ampulla (Hillemand, Beau and Bernard, 1953)  
inferior esophageal sphincter
4. *Transverse Mucosal Fold (TMF)*  
lower esophageal ring (Schatzki, 1953)  
Schatzki ring  
lower esophageal web  
lower esophageal diaphragm  
Ring B (Wolf, 1967)  
cardia (originally used by Thucydides—423 B.C.—and Hippocrates—430 B.C.—to denote cardiac end of the stomach)
5. *Sling Fibers of Stomach*  
A thick muscle band lying within the other gastric muscle layers which also marks the esophago-gastric junction at its left lateral margin. A smaller muscle band, the constrictor cardia, arises above it and encircles the esophago-gastric junction.  
sling fibers of Willis (Willis, 1674)  
muscle of Verheyen (1699)  
oblique fibers of stomach (Helvetius, 1719)  
collar of Helvetius  
Swiss Cravat  
bundle of His (His, 1903)

6. *Phreno-Esophageal Membrane*  
ligaments of Galen (Galen, A.D. 200)  
hiatal aponeurosis (Blandin, 1826)  
diaphragmatico-esophageal elastic membrane (Treitz, 1853)  
Laimer's membrane (Laimer, 1883)  
phrenico-esophageal diaphragm (Jonnescio, 1895)  
phreno-esophageal fascia (Le Double, 1897)  
phreno-esophageal fascial tube (Favera, 1906)
7. *Cardiac Notch*  
incisura cardia (His, 1903)
8. *Fundus of Stomach*  
apex of stomach
9. *Margin of Esophageal Hiatus in Diaphragm*
10. *Diaphragm*



Figure 2.—Sliding hiatal hernia. The entire vestibule is intrathoracic and lies above a pouch of herniated stomach. The upper and lower vestibular boundaries, the inferior esophageal sphincter (solid arrows), and transverse mucosal fold (open arrows) respectively, are visualized. Thick mucosal folds are present in the herniated gastric pouch. (Through courtesy of McGraw-Hill publishers, "Diagnostic Radiology—A Companion to Harrison's Principle of Internal Medicine," P. Ruben Koehler, M.D., editor.)

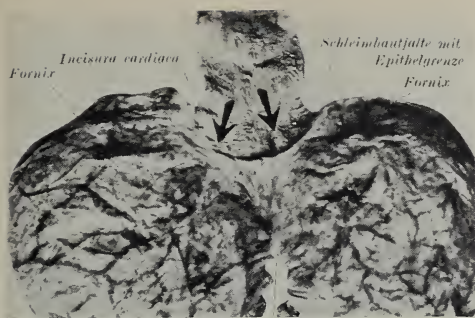


Figure 3.—Transverse mucosal fold. Specimen of normal esophagus and stomach which has been distended and fixed. A transverse mucosal fold is present at the esophago-gastric junction. (Through courtesy of Dr. Heinrich Hayek and the publishers, Springer-Verlag, Berlin, from—*Zeitschrift für Anatomie und Entwicklungsgeschichte* 100: 218-255, October 1933.)

stripes on a radiograph.<sup>17</sup> As the vestibule distends, the folds are effaced. When a hiatal hernia is present the vestibule is completely displaced into the thorax and the gastroesophageal junction is demarcated by a transverse mucosal fold which forms at the distal vestibule<sup>5,17,23</sup> (Figures 1, 2 and 3). This fold, which is seen as a thin ledge-like transverse ring, is not identifiable on a roentgenogram of a normal barium-filled esophagus and stomach.

The esophageal body, lying between the two sphincteric segments, may be conveniently divided into proximal, middle and distal thirds. The junction of the proximal and middle thirds is near the aortic arch as viewed roentgenographically.

### Normal Esophageal Physiology

The upper esophageal sphincter maintains a relatively high resting pressure (10 to 30 mm of mercury) when closed as compared with the adjacent intrapharyngeal and intraesophageal pressure.

The vestibule also has a higher resting pressure (15 to 35 mm of mercury) than the adjacent intraesophageal and intragastric pressures.

The highly integrated mechanism of deglutition transfers material from the mouth into the pharynx and then through the pharynx and esophagus to enter the stomach. The autonomic nervous system coordinates the entire sequence of neuromotor events.

Deglutition initiates a wave of inhibition, controlled centrally by a medullary swallowing center and mediated via the glossopharyngeal and vagus

nerves, that progresses aborally through the pharynx and esophagus at a speed of 10 to 20 cm per second.<sup>26</sup> Consequent to the wave of inhibition, the high resting pressure of the closed upper esophageal sphincter drops abruptly (relaxes) within 0.2 to 0.3 seconds after swallowing. Following upper sphincter relaxation, the wave of inhibition sweeps down the esophageal body to reach the closed vestibule 1.5 to 2.5 seconds after deglutition. The vestibule then also relaxes.

Following the wave of inhibition, a peristaltic wave traverses the pharynx and esophagus. This wave reaches the relaxed upper esophageal sphincter about 1 to 1.5 seconds after swallowing. The sphincter contracts, in peristaltic sequence with the pharynx above and the esophagus below, as the peristaltic wave passes through it. The wave sweeps down the esophagus at a rate of 2 to 4 cm per second with a mean amplitude usually ranging from 20 to 50 mm of mercury. When peristalsis reaches the relaxed vestibule, this sphincter also contracts.

As the sphincters contract, they close with return of their high resting pressures which reestablish them as protective barriers at both ends of the esophagus. Closed sphincters maintain their physiologic, high pressure barrier by resisting distension<sup>22</sup> thereby preventing inadvertent collections of saliva and food in the esophagus and gastroesophageal reflux. Sphincter relaxation during deglutition, however, allows a bolus to enter the esophagus and stomach without resistance.

Esophageal peristalsis may be defined as a lumen-obliterating contraction, about 4 to 8 cm in length, moving at 2 to 4 cm per second.<sup>26</sup> Two types of esophageal peristalsis occur. Primary peristalsis is initiated by deglutition and secondary peristalsis occurs in response to local esophageal stimulation. The most common stimulus initiating secondary peristalsis is esophageal intraluminal distension. Material left behind in the esophagus following a primary peristaltic wave or material from gastroesophageal reflux is transported to the stomach by secondary peristalsis. Once elicited, both types of peristalsis appear similar and travel down the esophagus whether or not a bolus is being transported.

Esophageal response to swallowing or distension is variable in normal adults. Although swallowing and esophageal distension usually elicit peristalsis, the response is inconsistent with respect to incidence, force or extent of propagation. The in-



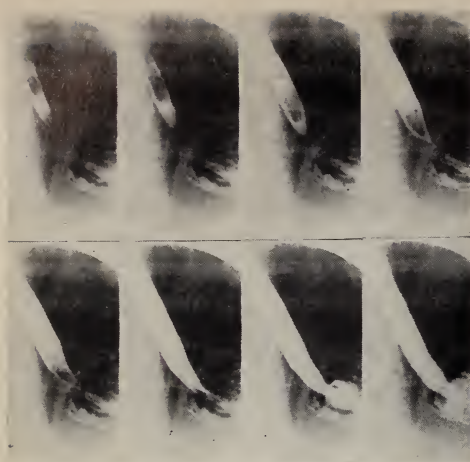


Figure 4.—Roentgenographic appearance of vestibular relaxation. With patient supine, serial 70 mm spot films were taken of the lower esophagus during a two-second interval immediately after deglutition of barium. The head of the barium column reaches the vestibule before its relaxation and assumes a V configuration (frames 1 and 2). The empty segment between the V and the stomach represents the vestibule. As the vestibule relaxes, barium flows through its lumen to enter the stomach. (Through the courtesy of W. B. Saunders Company, publishers, Radiologic Clinics of North America 7:147-161, April 1969.)

cidence and extent of propagation are less in the aged than in young adults.

Esophageal motor activity may be evaluated roentgenographically, either during fluoroscopy or on cineradiographic examination. The patient should be in the prone right anterior oblique position for evaluating esophageal motility. Following deglutition of barium, the contrast medium is distributed in a relatively continuous column throughout the esophagus. Because the upper esophageal sphincter relaxes promptly after swallowing, barium meets little resistance as it is propelled into the esophagus by buccopharyngeal dynamics. The barium column usually reaches the distal esophagus before vestibular relaxation occurs. In this circumstance, the barium encounters momentary delay before entering the stomach, and the head of the barium column adjacent to the closed vestibule assumes a "V" configuration (Figure 4). The point of the "V" demarcates the proximal margin of the vestibule. As the sphincter relaxes, the barium flows through it into the stomach. The vestibule may also be identified roentgenographically when relaxed and fully distended with barium. The intrathoracic portion then has a greater

caliber than the adjacent esophagus above; and, during inspiration, the intrahiatal segment is slightly narrower than the intrathoracic portion. The vestibular responses to deglutition and inspiration, as manifested during roentgenographic and intraluminal manometric examination, are summarized in Table 1.

When primary peristalsis occurs, it causes the upper end (tail) of the barium column to assume an inverted "V" configuration. The lumen obliterating peristaltic wave is then visualized as a progressive movement of the inverted V-shaped tail down the esophagus (Figure 5).

Peristalsis is not the only muscular contraction that occurs in the esophagus. A muscular contraction, whether annular or segmental, that occurs simultaneously during manometric examination is termed a nonperistaltic contraction. Roentgenographically, this contraction simultaneously displaces barium both orally and aborally from the contraction site. Muscular activity representing repetitive nonperistaltic contractions also occurs.

TABLE 1.—*Vestibular Responses to Deglutition and Inspiration*

#### *Deglutition*

##### *Radiology:*

- (1) vestibule opens
- (2) vestibule increases in length and width (lengthening of transverse and longitudinal muscles)
- (3) vestibule rises until almost entire length lies in thorax
- (4) when fully distended, intrathoracic portion of vestibule is wider than esophagus above
- (5) longitudinal mucosal folds effaced as vestibule opens

##### *Intraluminal Manometry:*

- (1) high resting pressure is ablated

#### *Inspiration*

##### *Radiology:*

##### *Hiatus\**

- (1) slides down on esophagus
- (2) moves forward
- (3) narrows
- (4) rotates to left

##### *Vestibule*

- (1) vestibule stretches
- (2) on full inspiration, most of vestibule lies in thorax
- (3) intrahiatal portion of vestibule is slightly narrower than intrathoracic portion

##### *Intraluminal Manometry:*

- (1) pressure in intra-abdominal portion of vestibule increases
- (2) pressure in intrathoracic portion of vestibule decreases

\*This has been demonstrated experimentally by marking the hiatus.

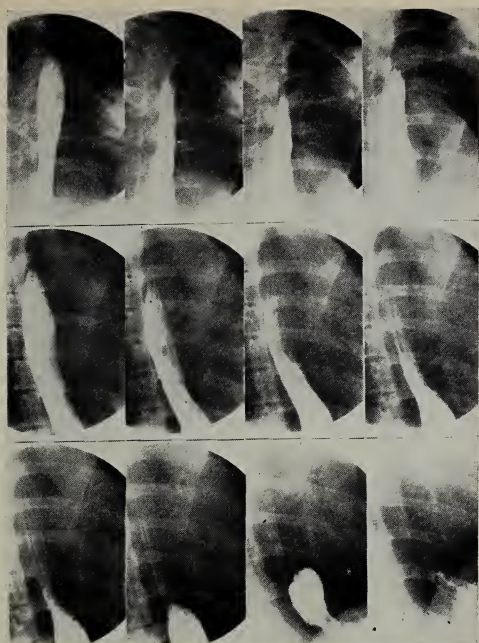


Figure 5.—Roentgenographic appearance of normal peristalsis. With patient supine, serial 70 mm spot films were taken during a 4.5 second interval following deglutition of barium. The x-ray tube was shifted slightly caudal after frames 3 and 10. Peristalsis causes the tail of the barium column to assume an inverted V shape. The peristaltic wave is visualized as a progressive aboral movement of the inverted V through the esophagus. (Through the courtesy of W. B. Saunders Company, publishers, *Radiologic Clinics of North America* 7:147-161, April, 1969.)

Their roentgenographic counterpart, termed tertiary contractions, cause the barium-filled esophagus to have an irregular, wrinkled contour. This appearance has also been called "curling" (Figure 6).

The cause of nonperistaltic contractions, single or repetitive, is not known. Their occasional occurrence in normal adults, however, denotes disorganization of the highly integrated mechanism of deglutition, albeit temporary.

In normal young adults 90 percent or more of swallows initiate primary peristalsis. Nonperistaltic contractions usually follow less than 10 percent of swallows, but emotional influences<sup>32</sup> and advancing age<sup>40</sup> may increase their incidence. Repetitive nonperistaltic contractions are not noted in young adults although they do occur in response to 10 percent or less of swallows in middle-aged adults.<sup>14</sup> Vestibular relaxation occurs after more than 95

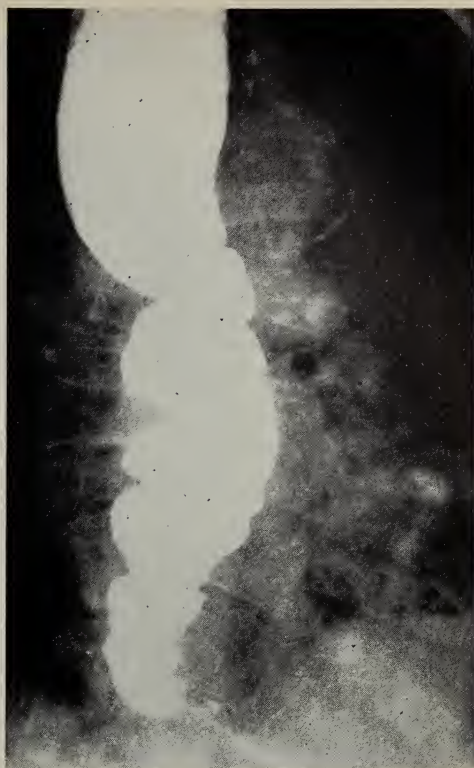


Figure 6.—Presbyesophagus. Tertiary contractions involve the lower one-half of the esophagus. Esophageal dilatation is prominent.

percent of swallows in normal young adults. This incidence decreases slightly with aging.

### Primary Esophageal Motility Disorders

A growing number of conditions resulting in abnormal neuromuscular esophageal function are now recognized. Such motility disorders may be classified as primary, the esophagus being the primary organ involved, or secondary to disorders which manifest associated esophageal abnormalities and to physical, chemical or pharmacologic effects on the esophagus.<sup>43</sup> In this review only the primary motility disorders (achalasia, diffuse esophageal spasm and presbyesophagus) will be discussed.

In esophageal motility disorders, the peristaltic mechanism and sphincter function are altered either singly or in combination.<sup>43</sup> Manometrically, abnormalities of primary peristalsis include com-



plete inability or decreased incidence of peristalsis being initiated by swallowing and the inability of the peristaltic waves, once initiated, to progress to the stomach. When peristalsis fails to traverse the entire esophagus, but "breaks" at some level, either no muscular activity or nonperistaltic contractions occur distally. All these abnormalities are assessable by roentgenographic examination. The integrity of secondary peristalsis cannot be evaluated roentgenographically as it is not possible, during routine examination, consistently to produce localized esophageal distension.

Significant clinical abnormalities of sphincteric function in primary motility disorders are confined to the vestibule. Roentgenographic assessment of vestibular function is usually limited to determining whether or not relaxation occurs and, if so, its incidence. Incomplete vestibular relaxation may be suggested.

If barium is retained above the closed vestibule longer than 2.5 seconds after deglutition, the vestibule has failed to relax. The barium column then remains above the vestibule until the pressure generated by an advancing peristaltic wave or nonperistaltic contraction above, and transmitted through the barium column, overcomes the resisting vestibular pressure. Barium then forces the vestibule slightly open and squirts into the stomach.

If incomplete vestibular relaxation occurs, the lumen does not open as widely as normal. It is often difficult, however, to determine whether a narrowed vestibule is caused by incomplete relaxation, failure of relaxation or stricture secondary to esophagitis.

In the absence of esophageal muscular contraction and vestibular relaxation, barium will traverse the vestibule only if the patient is placed erect allowing the hydrostatic pressure of the resultant vertical barium column to overcome vestibular resistance. The barium will then force the vestibule to distend slightly, allowing barium to enter the stomach.

### *Achalasia*

Achalasia usually has an insidious clinical onset, and though occurring at any age, frequently develops between 30 and 50 years of age. No sex predilection exists. The main symptom is dysphagia which, early in the disease, is frequently intermittent but later becomes persistent. Regurgitation, particularly at night, occurs commonly. Pain is a less frequent symptom.

Although etiologically obscure, achalasia is generally thought to be caused by an esophageal cholinergic innervation defect. The primary defect has been considered to be an absence or decrease of ganglion cells of Auerbach's myenteric plexus. However, this finding is not consistent and recent esophageal ultrastructure studies have demonstrated vagus nerve changes resembling Wallerian degeneration<sup>10</sup> and decreased cell counts of the medullary dorsal motor nucleus.<sup>8</sup> These features suggest that the primary defect is in the peripheral vagus nerve or dorsal motor nucleus and that esophageal changes are secondary.<sup>8</sup>

Utilizing intraluminal manometric recording techniques, achalasia is characterized by absence of peristalsis and failure of vestibular relaxation after deglutition<sup>21</sup> and by a positive Mecholyl®\* test.<sup>29</sup> The Mecholyl® test is generally considered the confirming diagnostic test of classic achalasia. Following subcutaneous administration of Mecholyl®, 10 mgm or less, a positive test produces a tetanic nonperistaltic contraction of the distal one-half to two-thirds of the esophagus which causes a sustained increase in esophageal resting pressure of more than 10 mm of mercury. This response has been interpreted as demonstrating loss of esophageal cholinergic innervation. Positive Mecholyl® tests have also been recorded in diffuse esophageal spasm.<sup>27</sup>

Roentgenographically, achalasia is characterized by a persistent failure of the vestibule to relax and absence of esophageal peristalsis after swallowing contrast material. The upper esophageal sphincter, however, does relax after deglutition. Peristalsis, even occurring over a few centimeters of the upper esophagus, negates the diagnosis of classic achalasia.<sup>43</sup> Nonperistaltic or repetitive nonperistaltic (tertiary) contractions may occur in response to deglutition or spontaneously. The esophagus may be atonic in advanced cases. Esophageal dilatation of varying degree occurs secondary to the motor abnormalities.

Because the vestibule consistently fails to relax, the head of the barium column adjacent to the vestibule maintains a "V" configuration. Barium remains above the vestibule until pressure transmitted through the contrast column by nonperistaltic contractions in the esophagus above (or hydrostatic pressure if the patient is erect) overcomes the resisting pressure of the unrelaxed vestibule. The vestibule is then forced slightly open by the

\* Mecholyl® = methylcholine chloride





Figure 7.—Achalasia. As barium squirts through the unrelaxed vestibule, the V shape of the head of the barium column is elongated and assumed a bird-beak configuration. This appearance is not specific for achalasia.

barium and barium squirts into the stomach. When barium is forced into or through the sphincter in this manner, the head of the barium column retains a V shape but the point becomes elongated (Figure 7).

This roentgenographic appearance, likened to a bird beak, has been erroneously considered characteristic of achalasia. Any disorder wherein the vestibule consistently fails to relax after deglutition manifests such beaklike deformity roentgenographically.<sup>43</sup> Although no disease except achalasia is uniformly characterized by absence of vestibular relaxation, an occasional patient with presbyesophagus,<sup>40</sup> diffuse esophageal spasm<sup>14</sup> or connective tissue disorder<sup>13</sup> has had failure of vestibular relaxation recorded in response to all swallows during manometric examination. The vestibule may also have a bird-beak configuration when involved with an annular constricting carcinoma or stricture secondary to esophagitis. These entities may usually be differentiated from achalasia on the basis of the motility profile manifest in the esophageal body.

Recently, six patients were described who had esophageal motor disturbance not characteristic of recognized esophageal diseases.<sup>24</sup> In all of them the clinical manifestations were similar to those of achalasia. During intraluminal manometry, however, peristalsis or vestibular relaxation, or both,

were demonstrated after some swallows although the incidence was significantly reduced. The observers did not attempt to classify these patients into a single category of esophageal disease, as they did not manifest identical abnormalities. The investigators stated that these patients may represent examples of an esophageal disease the full expression of which is true achalasia.

Clinically significant primary esophageal motility disorders usually are readily classified into one of the recognized categories of esophageal disease. Occasionally, motor abnormalities occur that resist strict definition; they may well represent variations of true achalasia.

### *Diffuse Esophageal Spasm*

Diffuse esophageal spasm is characterized clinically by intermittent dysphagia or pain, or both. No sex predilection exists and patients usually are middle aged.

Pain frequently is recorded as moderate substernal discomfort but may be colicky or mimic angina.<sup>16</sup> Frequently, symptoms are caused or aggravated by eating but may occur spontaneously. Symptoms usually are not incapacitating but an occasional patient who frequently experiences severe symptoms when eating may lose weight because he fears eating.

Intraluminal manometry<sup>18</sup> demonstrates primary peristalsis to be consistently propagated through the upper one-third of the esophagus in about 25 percent of patients. In all other patients with this disorder, the incidence of peristalsis in this region is diminished; nonperistaltic or repetitive nonperistaltic contractions, frequently of prolonged duration and abnormally high amplitude, are the predominant motor response to swallowing. Nonperistaltic contractions, single or repetitive, invariably follow deglutition in the lower two-thirds to one-half of the esophagus. Rarely does peristalsis traverse the entire esophagus. Although the vestibule usually relaxes, consistent failure of relaxation has been recorded<sup>14</sup>

Frequently, the esophageal muscle is thickened, occasionally to 2 cm (normal, 2 to 3 mm), and thickening may extend from the distal esophagus to the aortic arch level or higher.<sup>18</sup> Histologically, smooth muscle appears relatively normal<sup>12</sup> and ganglion cells are present.<sup>18</sup>

Roentgenographically, peristalsis occurs in the upper esophagus in response to some, and occasionally to all, swallows. When peristalsis is elicited

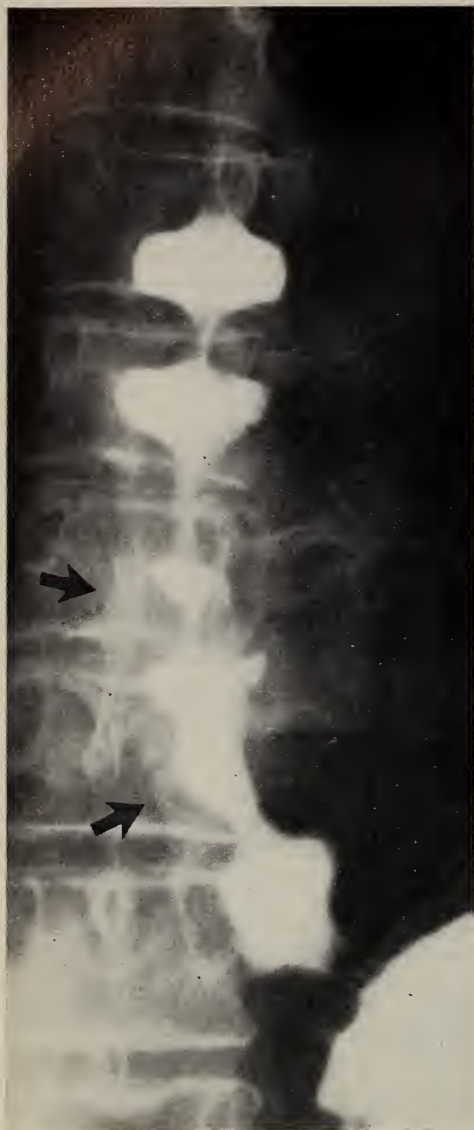


Figure 8.—Diffuse esophageal spasm. Tertiary contractions of abnormally high amplitude produce compartmentalization of the barium column. The esophageal wall is thickened (arrows). (Through the courtesy of W. B. Saunders Company, publishers, Radiologic Clinics of North America 7:147-161, April 1969.)

ed, its propagation invariably breaks about the level of the aortic arch and the lower esophagus responds with single or tertiary nonperistaltic contractions. If peristalsis does not occur in the upper

esophagus in response to deglutition, nonperistaltic contractions are elicited throughout the entire esophagus.

The abnormally high amplitude tertiary contractions produce compartmentalization of the barium column (Figure 8). This appearance is produced by barium being displaced both proximally and distally from the sites of highest generated pressure to adjacent areas where pressures attained during contraction are lower. This roentgenographic feature has been called "tiered spasms," pseudodiverticulosis, and the "rosary bead" esophagus.

Thickening of the distal one-third to two-thirds of the esophageal wall is often demonstrated roentgenographically. The lumen of the involved part of the esophagus may be narrowed; in these instances, the lumen of the uninvolved upper esophagus may be mildly dilated.

The cause of diffuse esophageal spasm is not known. Kramer, et al<sup>27</sup> recently demonstrated that most patients with this disorder manifest a hypersensitive esophageal response to Mecholyl®. They suggest that achalasia and diffuse spasm are related disorders because of their similar response to this cholinergic agent. Possible transition of diffuse esophageal spasm to achalasia has also been recorded.<sup>28</sup> Esophageal electron microscopy in achalasia and diffuse spasm by Cassella and colleagues,<sup>9</sup> however, suggest that the two diseases are separate entities. These investigators propose that diffuse spasm is characterized by primary involvement of the vagal afferent (sensory) system.

#### *Presbyesophagus*

Presbyesophagus is an esophageal motor dysfunction associated with aging. This motility disorder is usually noted in persons of geriatric age but it may be present in late middle age. Although geriatric patients may manifest a normal esophageal profile to deglutition, most reveal some abnormality. Patients usually have no esophageal symptoms; an occasional patient may have dysphagia when eating solids.

The predominant manometric esophageal abnormality is an inability to initiate primary peristalsis and vestibular relaxation.<sup>40</sup> The incidence of both responses is usually decidedly diminished. Propagation of primary peristalsis is also impaired. The decreased incidence of peristalsis following deglutition is accompanied by an increase in nonperistaltic



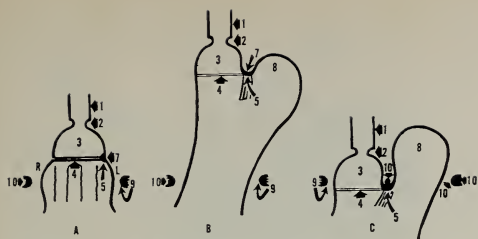


Figure 9.—Diagrammatic representation of the radiological anatomy of hiatal hernia.

A. *Small sliding hiatal hernia.* The vestibule (3) demarcated by the inferior esophageal sphincter (2) above, and the transverse mucosal fold (4) below, lies completely in the thorax above the hiatus (9). Below the vestibule is an intrathoracic sleeve of stomach, the walls of which are composed of a small portion of the lesser curve of the stomach on the right (R) and a small length of the fundus of the stomach on the left (L).

B. *Large sliding hiatal hernia.* The fundus of the stomach (8) lies in the thorax and balloons out to simulate its normal shape. The relative positions of the vestibule (3) and fundus (8) are similar to that seen when no hernia is present.

C. *Paraesophageal hiatal hernia.* The vestibule (3) maintains its normal relationship to the hiatus (9). The fundus of the stomach (8) rolls into the thorax either through the hiatus or through a separate opening in the diaphragm (10) immediately adjacent to the hiatus.

contractions, often repetitive, of normal amplitude. The Mecholyt® test is not positive.

A complete spectrum of peristaltic abnormalities is observed roentgenographically. Frequently peristaltic waves traverse only the upper esophagus, and occasionally no esophageal peristalsis is identified. The predominant roentgenographic feature is tertiary contractions, frequently involving a long esophageal segment<sup>41</sup> (Figure 6).

The vestibule may demonstrate a normal or decreased incidence of relaxation following deglutition or it may consistently fail to relax. Patients with significant motor dysfunction frequently have uniform esophageal dilatation which usually is moderate but may be prominent (Figure 6).

The roentgenographic features of presbyesophagus may occasionally resemble diffuse esophageal spasm, connective tissue disease, esophagitis and, rarely, achalasia.<sup>42</sup> Other diagnostic procedures may then be required before definitive diagnosis is possible.

## Hiatal Hernia

Two types of hiatal hernia occur, sliding and paraesophageal. Hiatal hernias may occur in infancy but are most common in adult life; they increase in incidence with age.

Sliding hiatal hernia, also known as axial, concentric or short esophagus type hernia, is most common. In sliding hiatal hernia, the entire vestibule lies within the thorax above an intrathoracic sleeve of stomach which has also herniated from the abdomen. If the hernia is small, the intrathoracic gastric sleeve, composed of a portion of fundus, usually forms a tube or pouch directly below the vestibule (Figures 2 and 9 A). If the hernia is large, the gastric fundus slips entirely into the thorax and balloons out to the left of the vestibule where it assumes its normal shape (Figure 9 B).

True paraesophageal hiatal hernias are uncommon at any age. These are also referred to as para-hiatal or rolling hiatal hernias. In these the vestibule maintains its normal anatomic relationship to the hiatus. The esophagogastric junction remains *below* the diaphragm, but part of the stomach herniates into the chest *alongside* the esophagus. The stomach may herniate either through the hiatus or through a separate diaphragmatic opening adjacent to the hiatus (Figure 9 C).

## Sliding Hiatal Hernia

Radiologic diagnosis of sliding hiatal hernia has traditionally been divided into two parts: (1) demonstrating the abnormal radiologic anatomy and (2) demonstrating gastroesophageal reflux of barium.

Although a sliding hiatal hernia is occasionally seen when the patient swallows barium standing upright (irreducible or fixed hernia), it is best demonstrated by having the patient prone over a bolster placed below the twelfth rib. By increasing intra-abdominal pressure, this procedure forces the stomach into the thorax. It also ensures maximum distension of the distal esophagus after the patient swallows barium.

If a normal patient lies prone over a bolster and swallows a thick barium bolus, most of the vestibule rises into the thorax, but the distal-most portion remains intra-abdominal. Similarly, if a normal patient inspires maximally, the hiatus slides down the esophagus, but again the distal vestibule remains in the abdomen. During both maneuvers, the stomach does not herniate above the hiatus.<sup>6</sup>

If the hiatus were demonstrable on radiographs, little problem in diagnosing hiatal hernia would occur. Unfortunately, the hiatus is not observed roentgenographically. The position of the hiatus may be inferred when a hernia is present because



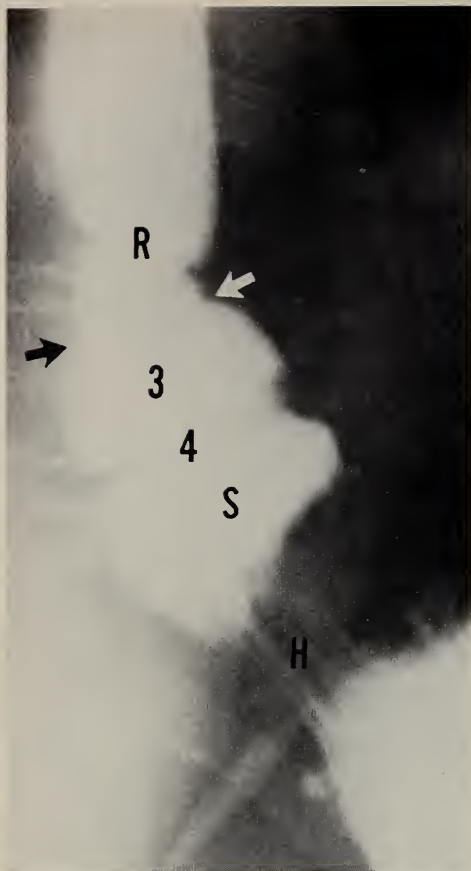


Figure 10.—Esophageal ring (stricture) located above the vestibule. Rigid, thin circumferential ring (R) is present above vestibule (3). Arrows indicate position of inferior esophageal sphincter. A hiatal hernia exists because vestibule (3), transverse mucosal fold (4) and portion of stomach (5) lie in thorax above hiatus (H). The intrahiatal stomach is so compressed by the hiatal margins that the gastric mucosal folds are squeezed together.

the hiatal margins may compress the intrahiatal stomach (Figure 10), but this feature is neither consistently present nor sufficiently reliable to be of diagnostic value.

In a small sliding hernia, the abnormally located gastric sleeve has a different configuration than normal stomach. The herniated stomach assumes a tubular or fusiform shape. Because a small hernia and the normal vestibule often have a similar configuration, it usually is impossible to distinguish them accurately by shape alone. Since it is difficult to identify the position of the hiatus and

to recognize a small intrathoracic gastric sleeve by its shape alone on roentgenographic examination, other criteria must be used to diagnose a small sliding hiatal hernia.

The presence of a small sliding hiatal hernia may be accurately diagnosed if the transverse mucosal fold is demonstrated.<sup>5,6,17</sup> This fold, a thin, ledge-like ring, forms the distal vestibular boundary, thereby demarcating the gastroesophageal junction (Figures 2, 3 and 10). When the gastroesophageal junction is located intra-abdominally, the transverse mucosal fold is not roentgenographically demonstrable; however, it does produce a roentgenographically identifiable structure when it is intrathoracic. Thus, the fold can be seen in all patients with sliding hiatal hernia. The fold is best seen when the vestibule is maximally distended with barium (Figures 2 and 10); it disappears as the vestibular lumen closes. To aid accurate identification of this anatomic landmark it is helpful if the upper vestibular boundary—that is, the inferior esophageal sphincter—also be demonstrated, as it may resemble the transverse mucosal fold. This sphincter also produces a ringlike deformity of the barium column (Figures 2 and 10) but does not indicate the presence of hiatal hernia because this portion of the vestibule is normally located in the thorax. This sphincter or ring can be demonstrated in most patients whether or not a hiatal hernia is present. The ring is best identified when the patient swallows barium while lying prone over a bolster or when the barium's consistency is similar to that of masticated solid food. The ring has rounded margins and is most prominent when the esophageal lumen at this site is only partially distended. When the sphincteric lumen is almost completely open, the ring is visualized as a slight transverse luminal indentation which may be difficult to distinguish from the transverse mucosal fold. The indentation disappears when the vestibule (sphincter) is completely open.

The above described landmarks may be difficult to record roentgenographically, for they appear but fleetingly during the passage of barium through the lower esophagus and vestibule, but an experienced fluoroscopist can usually identify them. Continual recording by cinefluorography permits the entire sequence of the esophageal study to be replayed and reviewed at a later time, thus aiding identification of anatomic details.

The mucosal pattern may also aid in differentiating the normal vestibule from herniated stomach.

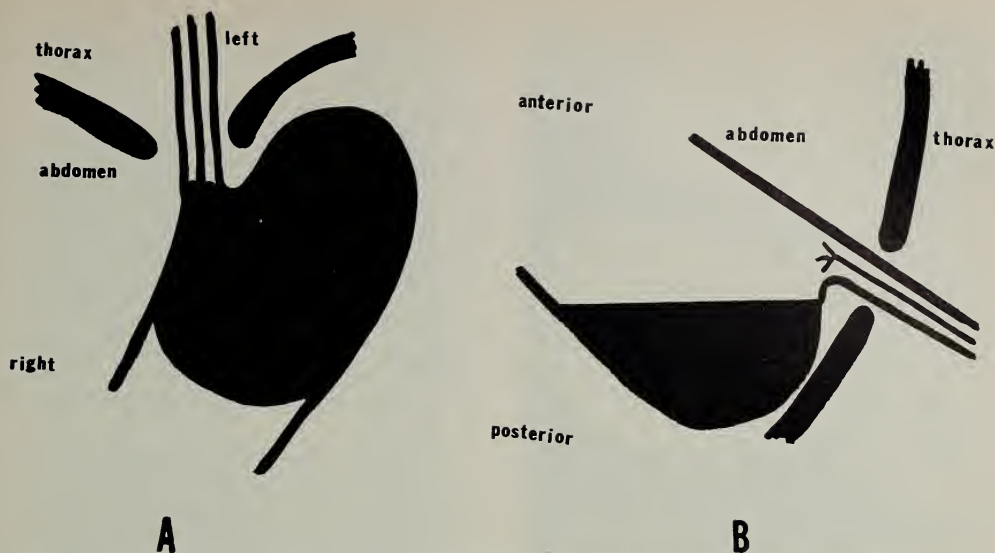


Figure 11.—Relationship of barium pooled in the gastric fundus to the esophago-gastric junction.

A. Appearance on posteroanterior or anteroposterior roentgenogram falsely suggests that barium in the stomach is covering the esophago-gastric junction.

B. True situation is demonstrated by horizontal x-ray with patient in same position. Barium pool is too shallow and does not cover the esophago-gastric junction.

The normal closed vestibule presents two to four fine, vertical, roughly parallel folds, whereas a herniated tube of stomach often has numerous thick, coarse mucosal folds (Figure 2). This distinction frequently is not possible, however, because gastric mucosa in a hernia may be stretched and thinned.

The radiologic diagnosis of a large sliding hiatal hernia usually presents no difficulty. It may be discovered on a routine chest roentgenogram. Large sliding hernias may be surprisingly asymptomatic. Very large hiatal hernias (totally intrathoracic stomach) may present as an acute emergency with gastric volvulus.

When either a small or large sliding hiatal hernia is present, the cardinal functional abnormality that may occur is gastroesophageal reflux. Many radiologists and clinicians feel it obligatory to demonstrate gastroesophageal reflux to prove the presence of a hiatal hernia. To demonstrate reflux, the patient frequently is subjected to a wide variety of gymnastic maneuvers. Examples: With the patient prone or supine the radiographic table is tilted head down; or the patient is called upon for straight leg raising while supine, or for crouching in the genupectoral position, or to touch his toes while erect; or pressure may be applied to the ab-

domen of the supine patient. Unfortunately there are several pitfalls in the interpretation of these tests. First, to demonstrate esophageal reflux it is essential that barium in the gastric fundus cover the esophago-gastric junction. The various positions described above were designed to produce this distribution of barium, but, unfortunately, neither anteroposterior nor posteroanterior roentgenograms provide certainty that this has been achieved. Whatever the patient's posture, only a horizontal x-ray beam will demonstrate whether or not the barium is covering the esophagogastric junction (Figure 11). Second, the hiatus may so compress the herniated sleeve of stomach passing through it that the gastric mucosal folds are squeezed together (Figure 10). These folds (the gastric mucosal choke) may then prevent reflux during the roentgenographic examination.

Further, standard barium preparations, unlike gastric juice or food, have a high specific gravity (6 or 7) and therefore reflux of barium may not occur during examination even though the hernia may allow reflux of gastric juice or food at other times. Recently Sandmark<sup>36</sup> demonstrated that standard barium may not reflux when a hernia is present whereas reflux may occur when a barium preparation of low specific gravity is used.

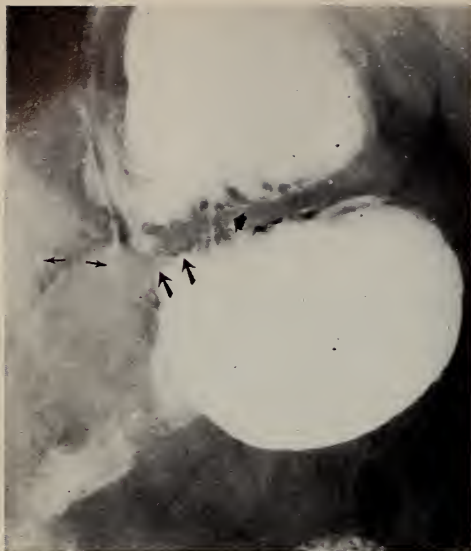


Figure 12.—Paraesophageal hiatal hernia. The esophago-gastric junction (2 large arrows) lies in its normal anatomical position. Most of the gastric fundus has herniated into the thorax. The gastric mucosal folds are squeezed together, thinned and straightened by the diaphragm (single arrow). The aorta is calcified (2 small arrows) and lies behind the esophago-gastric junction but overlaps the lower thoracic esophagus.

Some radiologists test for reflux from the barium-filled stomach by having a recumbent patient drink water. Because deglutition causes vestibular relaxation, this technique may allow transient esophageal reflux to occur even when no hernia exists. If such reflux is considered to indicate the presence of a hiatal hernia (usually it is so interpreted), the technique then causes false positive results.

Because of these various factors, demonstration of gastroesophageal reflux is not necessary to prove a hernia present. Moreover, gastroesophageal reflux is dependent on so many variables that it is an unreliable test as usually performed. Both false positive and false negative results are possible under certain conditions.

#### *Paraesophageal Hernias:*

In paraesophageal hernias the esophagogastric junction remains below the hiatus and the vestibule is normally located, but a pouch of stomach extends alongside the esophagus into the thorax (Figure 12). Gastroesophageal reflux does not occur and the major complications are related to vascular congestion and ulceration in the herniated

gastric fundus. Sometimes the herniated fundus may not fill with barium; the diagnosis is then usually missed.

#### *Esophagitis*

Esophagitis is classified as acute and chronic. Acute esophagitis may be caused by gastroesophageal reflux of acid-peptic juice, infectious agents, radiation and caustics. Patients usually are not examined roentgenographically during the early or acute phase of esophagitis. If esophageal barium studies are done, abnormalities usually are not identified. However, if inflammatory reaction and edema are sufficient, a lack of complete distensibility of the involved portion of the esophagus may be evident.

Chronic esophagitis is usually produced by recurrent gastroesophageal reflux: sliding hiatal hernias are present in most persons with this disorder. Clinical symptoms include heartburn, retrosternal pain, regurgitation and occasionally dysphagia. Controversy exists as to whether heartburn is due to chemical irritation<sup>4</sup> or abnormal esophageal motility.<sup>39</sup>

Chronic esophagitis may be manifested histologically by mucosal edema and erosion or, if more severe, mucosal ulceration associated with inflammatory edema of the submucosa or submucosa and muscularis externa. The latter response may produce thickening and decreased distensibility of the esophageal wall with resultant luminal narrowing. The narrowing is caused by inflammatory edema which produces wall thickening and limits esophageal distensibility. Narrowing may also be caused by stricture.

Esophageal motor dysfunction may be associated with chronic esophagitis. Motility abnormalities that may occur include incompetency of the lower esophageal sphincter and an absence or decreased incidence of peristalsis, accompanied by an increased incidence of nonperistaltic contractions, in the diseased esophageal segment.<sup>33</sup>

Neither superficial epithelial erosions nor mucosal edema are identifiable on roentgenograms. The only morphologic abnormality roentgenographically detectable is the luminal narrowing associated with thickening and decreased distensibility of the esophageal wall. This is usually characterized by a tapered symmetric narrowing of the involved segment without sharp demarcation between the abnormal and normal esophagus (Figure 13). Al-





Figure 13.—Chronic esophagitis. Lower esophageal lumen is symmetrically narrowed. The demarcation between normal esophagus and the involved segment is not sharply delineated.

though the narrowed lumen may close fully, it does not open completely.

Peptic esophagitis may occasionally be manifested roentgenographically as a fixed ring deformity of the esophageal lumen. This feature will be discussed under "Esophageal Rings."

Roentgenographic evaluation of esophageal motility may be normal. Frequently, however, primary peristalsis fails to traverse the segment involved with esophagitis and nonperistaltic contrac-

tions (single or tertiary) then make up the predominant motor response of the affected region. Recently, acid barium (pH 1.7) has been proposed as a means of inducing abnormal roentgenographic motility patterns in patients with esophagitis who demonstrate normal motility when a standard barium preparation is swallowed.<sup>15</sup>

### *Esophageal Rings*

An esophageal ring is a thin, circumferential indentation of the esophageal lumen. Descriptions of esophageal rings in the literature are very confusing but this is largely semantics. The main types of esophageal rings are classified in Table 2. Two rings are frequently observed in the lower esophagus: <sup>5,6,17</sup> an upper, the inferior esophageal sphincter, and a lower, the transverse mucosal fold (Figures 2 and 10).

Function of the inferior esophageal sphincter is unknown. Many radiologists regard it as a sphincter because it is capable of partial closure independent of the remaining vestibule. Anatomic studies suggest the ring is formed by esophageal muscle coat contraction.<sup>17</sup> When present it only partially occludes the lumen until peristalsis reaches it. It then closes completely as does the vestibule below. Most investigators are skeptical about considering this ring a sphincter because no high pressure zone is detected within it during intraluminal manometric investigation. It should be noted, however, that as the esophagus closes, its lumen, in cross-section, changes from a circular to a stellate configuration.<sup>17</sup> This permits a pronounced reduction of luminal flow to occur with only minimal change in pressure.<sup>11</sup> Thus, the inferior esophageal sphincter may have a sphincteric function when it produces a ringlike narrowing of the esophageal lumen. Inferior esophageal sphincter visualization does not indicate evidence of hiatal hernia or esophagitis. Transverse mucosal fold visualization indicates hiatal hernia; its presence does not imply esophagitis.

TABLE 2.—Classification of Esophageal Rings

1. Inferior esophageal sphincter
2. Transverse mucosal fold
3. Mucosal rings (diaphragms) secondary to localized peptic esophagitis
  - (a) at or near the transverse mucosal fold
  - (b) at or near the inferior esophageal sphincter
  - (c) elsewhere
4. Muscular ring approximately related to mucosal junction in a lower esophagus abnormally lined with columnar epithelium
5. Congenital



Figure 14.—Esophageal ring (stricture) at transverse mucosal fold. The vestibule (3) is fully distended and a hiatal hernia is present. Rigid ring (arrows) is located at the level of the transverse mucosal fold. It was demonstrated that the inferior esophageal sphincter was present and located proximal to the ring in other films. The luminal diameter of the esophagus at the site of ring formation is 1.0 cm.

Peptic esophagitis may cause thin, ledge-like mucosal diaphragms which protrude into the lumen and produce ring deformities. The rings are rigid, denoting localized stricture, and cause narrowing of the esophageal lumen (Figure 10). These mucosal diaphragms are usually single but, rarely, multiple mucosal diaphragms may develop in infants. The diaphragm usually develops at or near the transverse mucosal fold (Figure 14). When this occurs, the fold may not disappear as the vestibule closes and the lumen at this site may become very narrow. A barium-filled capsule or marshmallow may be unable to traverse the narrowed lumen. Clinically, the patient may complain of dysphagia. McMahon, Schatzki and Gary describe a patient who had dysphagia and a lower esophageal ring for nine years.<sup>31</sup> On histologic examination the ring, composed of mucosa, connective tissue and smooth muscle, was located at the gastroesophageal junction. Unfortunately, the term "Schatzki ring" is often used indiscriminately to describe any esophageal ring; because of this, the eponym should be abandoned.

Another common site for mucosal diaphragm formation is at or near the inferior esophageal sphincter but it may occur anywhere in the esophagus (Figure 10).



Figure 15.—Congenital esophageal ring. Esophagram requested in newborn period because the infant refused feedings. The thin, ledge-like diaphragm (arrows) is located in the lower esophagus.

Patients with an esophagus lined by columnar epithelium may develop esophageal stricture similar to that in patients with the more usual form of peptic esophagitis. The stricture is usually fibrous. However, the narrowing occasionally is not due to inflammation and fibrosis but is secondary to gross muscle thickening.<sup>3</sup> It then appears as a ring deformity.<sup>38</sup> Barrett describes this ring as





Figure 16.—Distal esophageal mucosa. The lower esophagus and upper stomach has been opened longitudinally. The junction between esophageal squamous and esophageal columnar epithelium is readily visible as an irregular "Z" line. The mucosal junction lies proximal to the esophagogastric junction. The longest digitation of squamous epithelium measures 1.5 cm. Longitudinal esophageal mucosal folds traverse both the squamous and columnar epithelial segments. In contrast to the longitudinal folds formed in the esophagus, gastric mucosa forms rugae. (Through courtesy of Norman R. Barrett, F.R.C.S., editor, *Thorax* 21:487-498, November 1966.)

having an appearance similar to the pylorus in congenital hypertrophic pyloric stenosis.<sup>3</sup> Although this ring may be situated anywhere in the esophagus, the involved area is frequently near the aortic arch region.

Congenital mucosal diaphragms are usually discovered in infancy and may occur anywhere in the esophagus (Figure 15). The cause is unknown.

### Peptic Ulcer

The esophagus is lined primarily with stratified squamous epithelium and the stomach by columnar epithelium. The junction between these two types of mucosa does not correspond to the esophago-gastric junction. A variable length of the distal esophagus is lined by columnar epithelium without parietal cells (Figure 16). This segment, usually about 0.75 cm long, is rarely more than 2.5 cm.

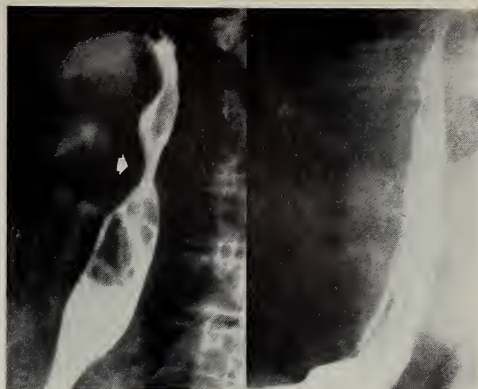


Figure 17.—Lower esophagus abnormally lined by columnar epithelium with esophageal stricture due to tryptic esophagitis. Total gastrectomy and esophago-jejunosomy seven years previously for gastric carcinoma. Severe symptoms of gastroesophageal reflux since operation. Recent onset of dysphagia. *Left*, esophagram demonstrates esophageal stricture (arrow) just distal to aortic arch. Esophagoscopy and biopsy revealed that the esophagus below the stricture was lined by columnar epithelium with a few abnormal villi, resembling jejunal mucosa. *Right*, mucosal pattern of lower esophagus (distal to the stricture) appears normal roentgenographically. (Through courtesy of Dr. F. Dick Berridge, Director, Diagnostic Radiologic Departments, The United Cambridge Hospitals, England.)

Barrett in 1950 described a condition wherein a greater length of lower esophagus is lined by columnar epithelium. The patients, usually middle-aged or elderly, invariably have hiatal hernia. Barrett subsequently called the disorder "lower esophagus lined by columnar epithelium."<sup>3</sup> Although the cause is not firmly established, it probably represents an unusual sequela of reflux esophagitis whereby columnar epithelium replaces squamous epithelium during healing. Rarely, a similar phenomenon occurs following total gastrectomy secondary to tryptic (alkaline) esophagitis (Figure 17).

Deep, chronic peptic ulcers may occur in an esophagus lined abnormally by columnar epithelium. The penetrating ulcers are well defined and easily recognized roentgenographically (Figure 18). The ulcer may erode a large vessel in the esophageal wall and produce massive hemorrhage.<sup>1,3</sup> Further, the ulcer may perforate the mediastinum, pleura, heart, aorta or pulmonary artery, again with the possibility of associated massive hemorrhage. In contrast to the deep ulcers occurring in this disorder, the erosions or ulcerations of squamous epithelium which occur in peptic esophagitis are not identifiable on roentgenograms.



Esophageal strictures may also occur in an esophagus abnormally lined by columnar epithelium. They usually present above the mucosal junction and frequently are in the upper esophagus near the level of the aortic arch (Figure 17, left). The triad of an esophagus abnormally lined by columnar epithelium, chronic peptic ulcer and esophageal stricture is called Barrett's syndrome. Adenocarcinoma may, on occasion, develop in the columnar epithelium.

An esophagus with normal squamous and columnar epithelium distribution may also occasionally develop penetrating peptic ulcer in the short terminal segment lined by columnar epithelium if hiatal hernia and reflux esophagitis are present.

### Carcinoma of the Esophagus

Esophageal carcinoma may be defined as to its site of origin. Thus, carcinoma may occur in the upper, middle or lower third of the esophagus. These areas correspond to or encompass the thoracic inlet, tracheal bifurcation and retrocardiac regions, respectively. However, carcinoma may develop anywhere in the esophagus, including the post-cricoid region, vestibule and esophago-gastric junction. The area near the tracheal bifurcation is most frequently involved. Esophageal carcinoma develops most often in elderly men. Post-cricoid lesions, however, occur mostly in women. An increased incidence of esophageal carcinoma is noted in persons with achalasia and post-cricoid webs associated with iron deficiency anemia (Plummer-Vinson syndrome).

Esophageal carcinomas are primarily of squamous origin, although adenocarcinoma may occur in the lower esophagus; these arise from esophageal columnar epithelium or from extension of gastric carcinoma into the esophagus. Adenocarcinoma may also develop in esophagus abnormally lined with columnar epithelium. A rare but distinct malignant lesion is carcinosarcoma wherein both squamous carcinoma and sarcomatous elements are present.

Esophageal carcinoma usually presents radiographically as an ulcer, polypoidal mass or annular constriction. Local spread, directly or by local lymphatic chains, may occur vertically or transversely. Vertical spread from the primary lesion via the rich esophageal wall lymphatic bed may occasionally produce secondary implantation sites, resulting in multiple, grossly noncontiguous carcinomas. Lymphatic spread may also occur to paraesopha-

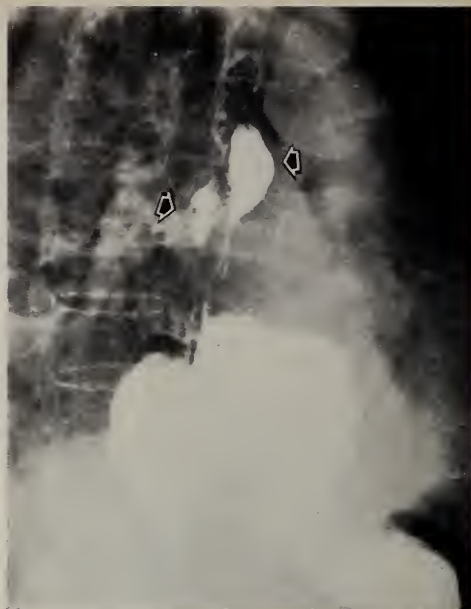


Figure 18.—Peptic ulcers of esophagus. 90-year-old male with a 20-year history of gastroesophageal reflux and recent onset of hematemesis and melena. Barium-air contrast study of the esophagus demonstrated large, penetrating esophageal ulcers (arrows) and a sliding hiatal hernia. At autopsy, the lower esophagus (including the areas of ulceration) was lined by columnar epithelium. The patient died from hemorrhage secondary to erosion of a large atheromatous artery at the base of the smaller ulcer. (Through the courtesy of Dr. F. Dick Berridge, Director, Diagnostic Radiologic Departments, The United Cambridge Hospitals, England.)

geal, tracheobronchial, supraclavicular and subdiaphragmatic nodes. Direct, vertical submucosal spread is frequent and often extensive. The transverse spread of tumor directly into the mediastinum, trachea, aorta, heart, mediastinal pleura and lungs also is frequent because no serosa surrounds the thoracic esophagus to impede its extension. Tracheal involvement may cause tracheoesophageal fistula and lead to lung abscess. When tumor penetrates the mediastinum, mediastinal abscess may result.

When carcinoma originates at or below the carina, 50 percent of patients have subdiaphragmatic node involvement at laparotomy.<sup>20</sup> Mortality is 100 percent when abdominal lymph node metastasis is present. Local extra-esophageal tumor spread is also associated with a grave prognosis. Hematogenous spread to liver, brain, bone, kidneys and adrenal glands may also occur.

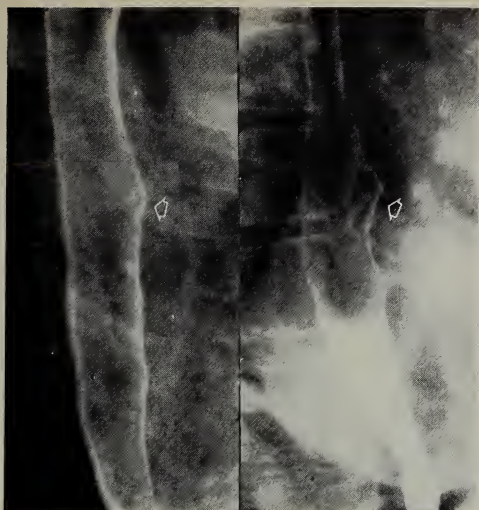


Figure 19. Small esophageal carcinoma. *Left*, slight asymmetry, straightening and rigidity of anterior esophageal wall (arrow) was demonstrated on barium swallow. *Right*, straight, rigid area (arrow) better defined after the patient was turned slightly.

The radiologist's responsibility in esophageal carcinoma includes differentiating malignant tumor from benign tumor or stricture, determining the extent of tumor, and assessing treatment results and complications.

Early esophageal carcinoma rarely causes symptoms. If radiologic examination is done when the lesion is small, it may be difficult to detect. A rigid area (Figure 19) or a small irregular or smooth filling defect should always suggest carcinoma (Figure 20).

Carcinomas present most commonly as annular constricting lesions. The constriction is characterized by a narrow, eccentric, rigid lumen with irregular nodular defects, sharply defined proximal and distal margins which appear "shouldered" and, frequently, tumor mass projecting outside the esophagus (Figure 21). An annular constricting carcinoma may, on occasion, resemble benign stricture from peptic esophagitis.<sup>19</sup> Usually, however, benign stricture has a smooth, concentric lumen, its proximal and distal margins taper gradually and smoothly to join the adjacent normal esophagus and no extrinsic tissue mass is present. Two other criteria may, on occasion, aid differentiation between a benign stricture and malignant constricting lesion.<sup>7</sup> Although both conditions may demonstrate a tortuous esophageal lumen, the rigid lumen of



Figure 20.—Small esophageal carcinoma (arrow) presenting as an irregular intraluminal filling defect.

a malignant lesion does not straighten on full inspiration whereas the lumen of benign stricture usually becomes straighter with deep inspiration. Further, a malignant constriction is usually so rigid that cardiac and aortic pulsations displace it whereas the more pliable walls of a benign stricture tend to be indented by such pulsations. When characteristic features exist, differentiation between malignancy and benignancy is easy. At times differentiation is impossible.

Polypoidal esophageal carcinomas are characterized by an irregular intraluminal mass (Figure 20). A carcinomatous ulcer, whether superficial or deep, is usually associated with and superimposed upon tumor mass. The rare carcinosarcoma characteristically is a large, well defined, lobulated, intraluminal mass, but it may present as an annular constricting lesion.

After having diagnosed esophageal carcinoma, the radiologist should attempt to determine the extent of tumor involvement beyond the confines of the esophagus. A number of radiologic techniques aid in determining mediastinal lymph node or tracheal involvement. Enlarged lymph nodes may





Figure 21.—Annular constricting carcinoma of the esophagus with mediastinal nodal metastatic lesions. An irregular, rigid constriction with “shouldered” edges and an associated soft tissue mass is present just distal to the carina. The extrinsic compression deformity (arrow) below the primary lesion was caused by a mediastinal lymph node, 1.7 cm in diameter, involved by tumor metastasis. (Through courtesy of McGraw-Hill publishers, “Diagnostic Radiology—A Companion to Harrison’s Principles of Internal Medicine,” P. Ruben Koehler, M.D., editor.)

cause a smooth, shallow indentation on the barium-filled esophagus distant to the tumor (Figure 21). Lateral chest tomograms and bronchograms may demonstrate tracheal involvement. If tracheoesophageal fistula occurs, the trachea is always infiltrated with tumor. To determine fistula forma-



Figure 22.—Zenker’s diverticulum. Lateral radiograph demonstrates the barium-filled pharynx (epiglottis identified by large arrow), diverticulum (small arrows) and upper esophagus. The diverticulum has displaced the esophagus forward. Because the diverticulum also lies lateral to the esophagus, it overlaps the barium-filled esophageal lumen. (Through courtesy of McGraw-Hill publishers, “Diagnostic Radiology—A Companion to Harrison’s Principles of Internal Medicine,” P. Ruben Koehler, M.D., editor.)

tion, the patient should swallow thin watery barium while in the prone position.<sup>4</sup> The presence of normal lung fields does not exclude fistula; 75 percent of patients with fistula have no radiologic pulmonary abnormality.<sup>34</sup> Posteroanterior and lateral chest radiographs may demonstrate mediastinal,



pulmonary or pleural lesions. Finally, pneumome-diastinography may be utilized to delineate tumor extent.<sup>25</sup>

If esophageal carcinoma is treated by radiation therapy, local eradication of tumor cannot be determined by diagnostic radiologic examination. An irregular narrowing usually remains following treatment, and whether this represents radiation esophagitis or residual carcinoma cannot be ascertained with certainty.

## Diverticula

Diverticula, although more common in the elderly, may occur at any age. Usually they have little clinical significance. They occur anywhere in the esophagus and frequently are found incidentally during roentgenographic examination. A large diverticulum may present as a posterosuperior mediastinal mass, with or without a fluid level, on a chest roentgenogram. Esophageal diverticula are easily recognized at fluoroscopy. They form saccular luminal outpouchings which vary in size from moment to moment.

A diverticulum may occur in the upper esophageal sphincter (Zenker's diverticulum). It is formed by a mucosal protrusion between the lower transverse and upper oblique cricopharyngeal muscle fibers. About 30 percent of people have a weak area between these muscle layers posteriorly (Kilian's dehiscence) through which mucosa may protrude.<sup>35</sup> Because expansion of the diverticulum is limited posteriorly, it deviates laterally and usually to the left; the esophagus is displaced forward and to the right (Figure 22).

Cinefluorography may demonstrate two abnormalities to be associated with Zenker's diverticulum:<sup>2,30,37</sup> (1) inefficient pharyngeal peristalsis and (2) closure of the cricopharyngeal muscle before pharyngeal peristalsis effects pharyngeal emptying.

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# Specialty Conferences

## Pyelonephritis and Associated Infections Of the Urinary Tract

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*This is the edited transcription of the regular teaching conferences in Infectious Diseases held weekly at the Harbor General Hospital, Torrance.*

### Introduction

LUCIEN B. GUZE, M.D.\*

AN ATTEMPT to describe the natural history of pyelonephritis might be likened to the fabled group of blind men examining an elephant—each trying to construct the whole from a limited examination. Thus, the pediatrician may see the infant with urinary tract infection as one who does not thrive properly and the older child as a problem of enuresis and psychological maladjustment. The obstetrician sees the same condition in his patient with “honeymoon” cystitis or, more seriously, in a woman with hypertensive complications of pregnancy. The gynecologist may be visited by this same patient after many deliveries and see urinary tract infection present as a cystocele with stress in-

continence and dysuria. The internist could see pyelonephritis as renal hypertension. Even worse, he may be confronted with a rapidly progressive “malignant” hypertension, a syndrome believed by some to be etiologically related to renal infection. The internist likewise could view pyelonephritis as chronic renal failure and thus become concerned with dialysis and the questions of transplantation. The urologist may see urinary tract infection in many forms and in a patient of any age—the phimotic infant, enuretic child, stone former, male with enlarged prostate, older female with narrowed, scarred urethra and intermittent dysuria, and always any person with evidence of vesicoureteral reflux. The urologist also has the unhappy responsibility of helping care for the paraplegic and noting the virtual certainty of urinary tract infection. Frequently it is this infection, with associated bacteremia and its consequences, which results in death of paralytic patients.

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There you have the perplexity: any specialist could describe pyelonephritis as he sees it, but it might not be the complete description. Therefore, today we have brought together a very knowledgeable and competent group of specialists in hope of presenting a better description of urinary tract infection in its many forms.

Clinical Comments

C. C. CALESCIBETTA, M.D.\*

THE INCIDENCE of infections of the urinary tract is second only to infections of the respiratory tract.<sup>1,2</sup> Urinary tract infections may involve the renal parenchyma or structures distal to it down to the urethra. Our ability to distinguish accurately between infection confined to the lower urinary tract and renal parenchymal involvement is limited and one cannot always equate bacteriuria with the latter.

The clinical manifestations of acute pyelonephritis are well known. Many patients will have symptoms of cystitis such as dysuria, frequency and urgency. Fever, chills and flank pain are common. In addition, nausea, vomiting, ileus, anterior abdominal pain and headache can occur. There is also a large group of asymptomatic patients with bacteriuria in whom laboratory studies are the only means of arriving at a diagnosis.

A significant bacteriuria has been defined as 100,000 or more bacteria per milliliter of urine on culture of properly obtained fresh voided midstream urine.<sup>3</sup> The epidemiologic studies of Kass<sup>4</sup> and Kunin and coworkers<sup>5</sup> point out the high frequency of bacteriuria in the general population. As an example, bacteriuria during pregnancy may occur in as high as 6 percent of patients and acute symptomatic pyelonephritis may develop in as many as 40 percent of such patients at some time during their pregnancy.<sup>6</sup>

An increased incidence of prematurity and perinatal mortality was noted in this group<sup>4,6</sup> but this finding was not confirmed by other observers.<sup>7</sup> There are many other conditions thought to be associated with increased susceptibility to urinary tract infections. Some of these are listed in Table 1. There are areas of controversy, especially with regard to diabetes mellitus, analgesic abuse and hypertension.<sup>6,8</sup> Urinary tract infection is both more frequent and severe in potassium depleted ani-

mals.<sup>9</sup> Increased susceptibility to renal infection may persist for some time after potassium deficit has been corrected.

Urine examination is a logical early step in the approach to a patient with suspected urinary tract infection. Although the procedure is simple, proper collection methods must be used if the bacteriological results are to be reliable. Collecting urine by the clean, voided, midstream technique is the method of choice. With this method a high degree of reliability can be obtained with two cultures.<sup>4,10</sup> Urethral catheterization is rarely necessary to obtain a urine specimen. It is preferable to use suprapubic bladder puncture to obtain urine specimens from infants and uncooperative patients. This technique is of proved value and safety.<sup>11</sup> When suprapubic bladder aspiration is performed, it is important to locate the bladder by percussion and palpation and to make sure it is distended.

Microscopic examination of urine can be very helpful. If urine is centrifuged, a standard method should be used—for example, 10 ml of urine in a centrifuge tube spun for 5 minutes at 1,500 RPM, supernatant decanted and sediment resuspended in approximately 0.5 ml of urine remaining. Staining the urine sediment with safranin and crystal violet has been employed by some investigators.<sup>12</sup> "Glitter cells," which are leukocytes with Brownian movement of the granules, are not pathognomonic but do raise suspicion of urinary tract infection.<sup>13</sup> Since urine osmolality of 600 mosm per kg or greater inhibits the glitter cell phenomenon, a negative finding is not very helpful. A positive correlation with renal parenchymal inflammation has been shown when pale staining leukocytes were present in the urine.<sup>14</sup>

Pyuria is a common finding although quantitative relationships between leukocyte excretion and bacteriuria are not well defined. Several investigators have used the hourly leukocyte excretion rate as a quantitative expression of pyuria. Although there is a wide range of normals, leukocyte excretion rates of 200,000 per hour or greater are considered significant of urinary tract inflammation only, and not necessarily of bacterial infection of

TABLE 1.—Conditions Associated with Increased Susceptibility to Urinary Tract Infections

Pregnancy	Sickle cell trait & disease
Congenital malformations	Hypokalemia
Vesico-uretral reflux	Analgesic abuse
Obstruction	Nephrosclerosis
Diabetes mellitus	Vitamin A deficiency
Gout	Hypertension

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renal parenchyma.<sup>15,16</sup> The presence of five leukocytes per high power field or more is considered abnormal on examination of a centrifuged urine sediment, but 21 percent of patients excreting 200,000 leukocytes or more per hour will have fewer than five leukocytes per HPF.<sup>15</sup> There are variables which can affect this determination—the volume of urine in the centrifuge tube, the volume of urine in which cells are resuspended, the volume of urine in which cells are excreted, and finally the thickness of film under the coverslip. Leukocyte casts, on the other hand, almost always mean parenchymal inflammation and great significance must be attached to their presence in the urine.<sup>17</sup>

Provocative tests to induce pyuria in patients with suspected renal tract inflammation, such as the "pyrexal" or prednisolone phosphate tests, have not been helpful<sup>18,19</sup> due to the occurrence of false negatives.

Examination of urine sediment for presence of bacteria is a quick and reliable way to diagnose urinary tract infections. By placing fresh, uncentrifuged urine from a 3 mm loop onto a glass slide, allowing it to dry and then Gram-staining it, Hoepfich found a good correlation with the streak plate method of culture, if bacteria were found after examining nearly all oil immersion fields.<sup>1</sup> This method appears too time-consuming. Kunin found a high degree of predictability when bacteria were found in the unstained centrifuged urinary sediment as routinely examined by most clinicians.<sup>20</sup> Staphylococci are very difficult to recognize in unstained urine, and staining of the sediment is necessary to rule out their presence. Phase contrast microscopy of unstained sediment permits a more rapid and reliable interpretation of formed elements than does standard light microscopy or special stains. This technique is being advocated by others and should be adopted as routine.<sup>21</sup>

The previously mentioned diagnostic maneuvers may provide presumptive evidence of urinary tract infection. Definitive evidence requires confirmation by urine culture. Again it must be stressed that the method of collecting the urine specimen requires adherence to a rigid protocol which ensures a "clean" specimen. The importance of this has been demonstrated by Stamey,<sup>22</sup> who showed that in 54 females with sterile bladder urine obtained by suprapubic needle aspiration, only 21 percent of these patients could actually obtain a sterile specimen by unsupervised, midstream collection and 7 percent had colony counts of 100,000

per ml or greater. Twenty-six of the cultures grew Gram-negative bacilli. When a carefully collected, supervised midstream aliquot was obtained from another group of 151 females with sterile suprapubic bladder aspirations, all patients with positive cultures had fewer than 1,000 organisms per milliliter of urine. Likewise in males, where urethral infection may be common cause of relapsing acute urinary tract infections, a midstream urine for culture is necessary. Separating the first 5 ml of voided urine in males from the remainder may help to localize the source of bacteria, if the first 5 to 10 ml of urine is considered urethral washout.

When the urine is collected it must not be allowed to remain at room temperature for more than 1 hour before culture. If it cannot be put on a plate within that time it should be refrigerated but not for more than 3 or 4 hours.

All culture techniques are based on the principle that 100,000 organisms per ml of urine is significant bacteriuria, that is, not due to contamination. It was shown by Kass<sup>23</sup> that 95 percent of patients with clinical pyelonephritis had counts of this order or greater. The pour plate method is the standard technique used for microbial enumeration. It is simple and relatively inexpensive. The streak plate method utilizes graduated loops instead of pipets to quantitate the amount of urine plated, is simpler and appears reliable.<sup>1</sup> A miniature plate culture technique has been developed which may prove very useful for office practice. A filter paper strip is dipped into urine, placed in a small rectangular disk filled with trypticase soy agar and incubated for 12 hours at 37°C (it is assumed a standard amount of urine will adhere to the filter paper). Using this method, Hobday<sup>24</sup> found one false negative in 39 infected specimens when compared with the pour-plate method. A dip-slide method has also been found to correlate well with the pour-plate technique.<sup>25</sup>

There are other indirect tests which have been advocated for detection of significant bacteriuria. The Greiss test, based on the principle that large numbers of bacteria will reduce nitrate to nitrite, has proved too insensitive, missing up to 49 percent of patients with positive cultures by the pour plate method, although other workers report an incidence of 21 percent false positives with this technique.<sup>26,27</sup> The Tetrazolium test (TTC), based on the observation that 2,3,5 triphenyl-tetrazolium is reduced to bright red triphenyl formozan in the presence of large numbers of bacteria, has proved

too insensitive with 14 to 44 percent false negatives.<sup>28,29</sup> A recent report utilizing the TTC method but relying on fresh reagents and prolonging the incubation period indicates that this can be a highly sensitive test which may have some use for screening purposes where more accurate methods are not available.<sup>30</sup> The presence of significant bacteriuria will reduce urinary glucose concentrations. This principle was used by Schersten and Fritz<sup>31</sup> to detect urinary glucose levels below 2 mg per 100 ml in 11 of 12 female patients with significant bacteriuria by pour-plate technique. This test cannot be used in diabetes for obvious reasons.

The presence of bacteria in bladder urine does not prove bacterial invasion of upper tracts or renal parenchyma. Stamey<sup>22</sup> in attempting to localize urinary tract infections in 95 females and 26 males with proved bladder infections found that in 40 percent of females and 62 percent of males the infection was limited to the bladder. Urine obtained by ureteral catheterization was used to rule out pyelonephritis and to determine if unilateral or bilateral pyelonephritis was present. As a routine measure, this approach is impractical and other methods of distinguishing bladder from renal bacteria are under investigation. Differences in serum bactericidal antibody, maximum urinary concentrating ability, radiographic examination and enzyme excretion may be of value in separating upper from lower tract bacteriuria.

Percival and associates<sup>32</sup> reported measuring antibodies in patients' serum by a bacterial agglutination test using the infecting organism as antigen. They suggested that the presence of renal parenchymal infection can be distinguished from bladder infection with this technique. Serial measurement of hemagglutinins to "O" antigens from bacteria in the infected urine has also offered promise in the documentation of urinary tract infections and in differentiating acute and chronic pyelonephritis from cystitis.<sup>33</sup>

It has been known for some time that patients with bacteriuria may be unable to concentrate urine normally.<sup>34,35</sup> A more recent report demonstrated a defect in maximal urine concentrating ability in patients with renal bacteriuria but not bladder bacteriuria, and also that this defect could be reversed by successfully treating the bacteriuria.<sup>36</sup>

The use of radiography in diagnosing pyelonephritis is helpful in late stages. Caliectasis, irregularity in outline of cortical surfaces and calyceal

tips are fairly characteristic features although not specific.<sup>22</sup> Renal biopsy has been of little value in the diagnosis of pyelonephritis because the typically focal nature of the disease makes the biopsy specimen not representative of the tissue at large.<sup>37</sup>

## Pathology and Physiology

RICHARD J. GLASSOCK, M.D.\*

MUCH OF THE present-day interest in the long-term effects of infection of the kidneys and urinary tract can be traced to the classic studies of Longcope and Winkenwerder<sup>38</sup> and Weiss and Parker<sup>39</sup> published more than 30 years ago. The concepts put forth by these investigators have had a great influence on the approach to the problem of infections of the urinary system.

The term *pyelonephritis* has come to mean the pathologic changes occurring in the kidney as a result of invasion of the renal parenchyma by pathogenic bacteria.<sup>40</sup> Great difficulty has been encountered in relating structural changes to defined pathogenetic mechanisms; indeed, the precise role of bacterial infection in the morphologic entity of chronic pyelonephritis is unclear.

It has become clear that there are few pathognomonic features of bacterial invasion of the kidney. Certainly, in the absence of localized abscess formation or the demonstration of bacteria within the affected tissue, the histopathologic changes in the kidney observed in pyelonephritis are non-specific. Similar changes may be observed in such diverse entities as nephrosclerosis, radiation nephritis, nephropathy of analgesic abuse, endemic Balkan chronic interstitial nephritis, hypercalcemic nephropathy, and sickle cell disease, to name a few. The wide variation in cited incidence of pyelonephritis at autopsy (0.6 percent to 33 percent<sup>40-45</sup>) may be in part an expression of the lack of unanimity among pathologists regarding the specificity of morphologic diagnosis of chronic pyelonephritis, although other factors such as age and sex of the population studied undoubtedly are important. A more reasonable approximation of incidence at autopsy, using strict morphologic criteria, is closer to 1 to 3 percent.

It may be worthwhile, however, to review briefly some of the pathologic findings described in chronic pyelonephritis. On gross study there is usually, although not invariably, irregular and

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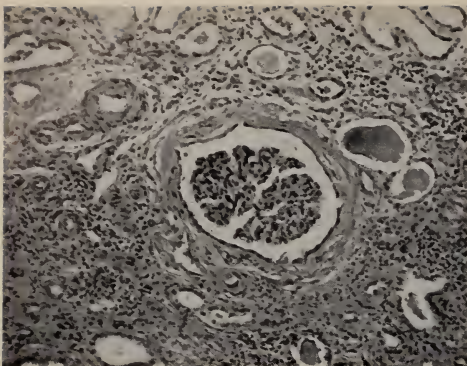


Figure 1.—Periglomerular fibrosis, interstitial fibrosis, tubular atrophy and mononuclear cell infiltrate in chronic pyelonephritis. H&E  $\times 250$ .

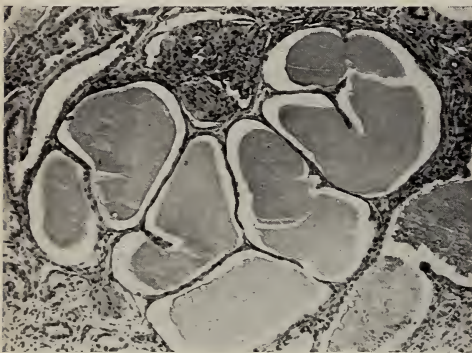


Figure 2.—Thyroid-like changes in chronic pyelonephritis. H&E  $\times 250$ .

asymmetrical scarring of the kidneys, often with deep U-shaped cortical scars. Extreme degrees of atrophy are not uncommon. Evidence of urinary tract obstruction or papillary necrosis may be observed. The gross examination is often important in differentiating the histologic lesions from other non-bacterial processes. Microscopically, variable degrees of interstitial inflammation and fibrosis (Figure 1) may be found. This inflammatory response is generally pleomorphic, containing plasma cells, mature and immature lymphocytes, histiocytes and, not infrequently, eosinophils. The presence of polymorphonuclear leukocytes in the interstitium or in the tubular lumina has generally been regarded as evidence of "active" disease. Interstitial fibrosis and tubular atrophy occur focally, often with normal parenchyma seen adjacent to a scarred area. Tubular basement membranes are thickened,

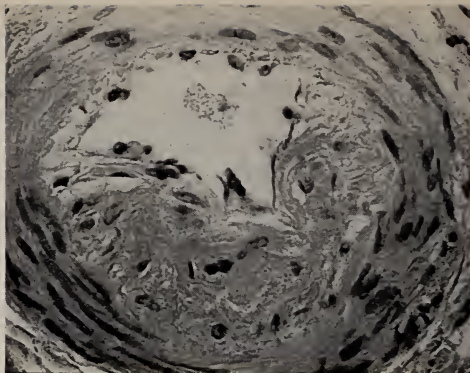


Figure 3.—Pronounced fibro-cellular intimal thickening of an interlobular vessel in a 21-year-old patient with chronic obstructive pyelonephritis and hypertension. H&E  $\times 400$ .

particularly in the areas of scar, and the occurrence of widely dilated tubules with atrophic epithelial cells with lumina filled with acellular eosinophilic material (Figure 2) has led to the designation "thyroidization," due to a similarity to thyroid tissue. Vascular lesions consisting of concentric and eccentric fibrocellular intimal proliferation in the arcuate and interlobar arteries (Figure 3) are seen frequently. The role of the vascular lesions in the hypertension frequently associated with pyelonephritis and the related tubular, glomerular and interstitial alterations seen which resemble an ischemic process, have been emphasized by Kincaid-Smith.<sup>46</sup> Glomerular lesions are later manifestations, but centrilobular hyalinization and gradual obsolescence occur, perhaps related to the vascular lesions. In the usual case it is not possible to demonstrate bacteria by conventional staining methods.

A thickened collagen matrix concentrically surrounding Bowman's capsule (periglomerular fibrosis) is also a feature frequently observed in pyelonephritis (Figure 1). Inflammatory changes found in the calyceal and pelvocalyceal areas and adjacent parenchyma are accepted by many as being a hallmark of infection as a cause of the observed renal parenchymal alterations.<sup>40</sup>

Many possible pathogenetic mechanisms have been proposed for the morphologic changes observed in chronic pyelonephritis. Active and persistent bacterial invasion of renal parenchyma with local damage to renal architecture is an obviously satisfactory explanation in many instances. Al-





Figure 4.—Cystogram showing bilateral vesico-ureteral reflux.

though there is no question that ascending or hematogenous bacterial invasion of the kidney can and does occur, the precise role in the causation of chronic disease remains unclear. Pawlowski and associates<sup>45</sup> were unable to demonstrate tissue infection consistently in an autopsy study of patients with pyelonephritis diagnosed clinically by strict criteria, even when specimens for culture were taken from obviously scarred areas of involved kidneys. Furthermore, clinical studies of percutaneous biopsy material have yielded positive cultures only in a small minority of cases.<sup>47</sup> It is important to note that in these and related studies cortical rather than medullary tissue was sampled and conventional media were employed for the isolation of bacteria. The latter point has come to have special significance as the result of the studies of Guze and Kalmanson.<sup>48</sup> These investigators demonstrated that certain bacteria (enterococci) can be converted to protoplasts by antibiotics, and presumably by other endogenous factors such as antibody and complement, through interference with cell wall synthesis. Survival of these proto-

plasts for long periods in the hypertonic medullary environment of animals has been demonstrated and such organisms will not be found in tissue homogenates unless special osmotically stabilized media are employed for their detection. Questions as to whether protoplasts are formed as a consequence of natural infection in an untreated patient and their role in human disease remain to be answered. The role of chronic viral infection of the kidney in the pathogenesis of chronic disease remains speculative although the recent demonstration of coxsackie B virus antigen in the kidney of some patients with chronic pyelonephritis<sup>49</sup> is a new and challenging avenue of research.

Persistent bacteriuria is not an invariable finding in patients fulfilling the pathologic criteria of chronic pyelonephritis; and, conversely, in the absence of obstruction or other known predisposing factors such as diabetes mellitus, the persistence of bacteriuria need not necessarily lead to chronic parenchymal destruction and loss of renal function. Kleeman and Freedman<sup>43</sup> pointed out that despite the absence of any significant difference in the incidence of pyelonephritis at autopsy between males and females the predominance of bacteriuria in females is consistent with the idea that factors other than bacterial infection may play an important role in the causation of chronic pyelonephritis as recognized at autopsy. Freedman also emphasized the frequency with which other etiological factors such as analgesic abuse, cystic disease of the renal medulla and sickle cell disease are found in cases thought to represent chronic bacterial pyelonephritis in the absence of diabetes or obstruction.<sup>41</sup>

Initial vascular damage, arterial and venous, brought about by acute bacterial infection and tissue invasion followed by chronic reparative changes could conceivably lead to ischemic alterations within the renal parenchyma. Many of the pathologic findings of chronic pyelonephritis are also found in benign nephrosclerosis. Bacteriuria and hypertension frequently coexist, but a cause and effect relationship remains to be established. It can be assumed that the vascular changes observed in chronic pyelonephritis contribute to some extent to some of the other morphologic features of the disease.<sup>39,40,46,50</sup>

Local intrarenal obstruction resulting from bacterial invasion and consequent acute damage to tubular architecture, particularly in the medulla, may be responsible for some of the chronic changes observed. Evidence of local intrarenal obstruction

occurs in both the disease of man and experimental animals and appears to be dependent to some degree upon the nature of the organism involved, proteus species being notorious for predisposing to urolithiasis and obstructive disease, particularly in experimental animals.<sup>51,52</sup>

Local or systemic immunologic processes initiated by an original episode of bacterial invasion and perpetuated even in the absence of continued infection with viable organisms have been demonstrated and may be pathogenetically important in the chronic disease. An immunologic explanation of the chronic progressive character of pyelonephritis has many attractive features. It has been shown in both man and experimental animals that bacterial antigens, presumably nonviable, can persist for long periods in the renal parenchyma even in the presence of sterile urine.<sup>52</sup> Furthermore, local synthesis of antibacterial antibody has been demonstrated by several techniques.<sup>53,54</sup> Circulating antibacterial antibody is also present but quantitatively does not correlate well with progressive disease.<sup>53</sup> The persistence of antigens and local and systemic antibacterial antibody synthesis provide the elements of an immunologic reaction at the site of bacterial antigen deposition. It is further possible that delayed hypersensitivity mechanisms, in which circulating or classical antibody responses are absent, may also play a role. The recent findings by Kalmanson, Sommers and Guze<sup>55</sup> of successful production of tubular damage in the recipients of lymphoid cells from pyelonephritic donors suggests that such cellular autoimmune factors may be important in the pathogenesis of chronic disease.

The changes in renal function observed in chronic pyelonephritis are likewise nonspecific although there is a tendency for impairment of maximal concentrating ability<sup>34,36,56</sup>, the excretion of acid<sup>34,57</sup> and an inability to efficiently conserve sodium<sup>34,58</sup> in this disease when patients are compared with those with primary glomerular disorders with similar degrees of impairment of glomerular filtration rate. However, as pyelonephritis progresses with steady decline in glomerular filtration the differences in pyelonephritis and diseases primarily affecting the glomeruli tend to be obscured by the functional adaptation of the kidney to the progressive loss of nephron mass, which results in a high solute load per nephron and a compensatory increase in glomerular filtration rate per remaining nephron.

Occasionally patients with pyelonephritis present as striking examples of "tubular defects." For example, instances of pronounced sodium wastage, proximal bicarbonate wasting and nephrogenic diabetes insipidus-like picture have been reported in presumed chronic pyelonephritis.<sup>59</sup>

The nature of the early impairment of maximal concentrating ability has been extensively studied.<sup>56</sup> Although the function of the medullary countercurrent system of urinary concentration is impaired, the precise mechanism is unknown. The concentration of sodium in the papilla is unchanged; however, urea concentrations fall in experimental pyelonephritis. The transport of sodium by the ascending limb of the loop of Henle is not affected. Possible mechanisms offered include an increase in medullary and vasa recta blood flow, an abnormality of permeability of the collecting duct epithelium, and disturbance in the architecture of the medulla and papilla leading to a failure of osmotic equilibrium between collecting duct urine and the hypertonic medullary interstitium.<sup>56</sup>

It should be pointed out that the findings in chronic pyelonephritis are different from those found in hypercalcemia and hypokalemia, where there is a diminished content of both sodium and urea in the papilla.<sup>56</sup>

An abnormality of sodium conservation is detected frequently in patients with diminished glomerular filtration rate regardless of the cause of their disease. Many patients with glomerular filtration rates less than 20 percent of normal have a potential defect in sodium conservation.<sup>58</sup> Pyelonephritis may be characterized by an earlier onset and greater severity of this potential sodium conserving defect.<sup>58</sup>

## Urology

ABRAHAM T. K. COCKETT, M.D.\*

MY PURPOSE as the urologist in this conference is to point out the importance of vesicoureteral reflux in the genesis of pyelonephritis. First, let me emphasize that vesicoureteral reflux is an abnormal occurrence.<sup>60</sup> Second, the phenomenon of reflux is important to the clinician in several ways: (1) It is a means by which infected urine can reach the pelvis and medulla. (2) The presence of reflux should set in motion an organized search for the presence of bladder or urethral outlet obstruction.

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In the majority of instances one can suspect a concentric bladder neck obstruction. However, the clinician's efforts cannot be discontinued until a mechanical cause has been carefully ruled out; this means that diagnostic studies of a urologic nature are imperative in ruling out the presence of an organic lesion. (3) Both bladder and ureters will decompensate with time in a refluxing patient. When decompensation occurs, detrusor tone for micturition decreases. Ultimately, the classical signs of cellule formation with diverticuli further disrupt bladder efficiency. The bladder decompensates by becoming thin-walled and atonic, the ureters become tortuous and kink because lengthening is the only response available to the ureter. Finally, severe hydronephrosis develops, culminating in renal insufficiency.

The urological evaluation of patients suspected of having vesicoureter reflux consists of watching the patient void. In the female this is not possible. Accordingly, cystography with voiding and gravity-dependent x-ray films are obtained. The addition of cinefluoroscopy is useful. Intravenous urography must follow cystography. We have been impressed with the number of congenital abnormalities present in the pediatric age group. Two such cases are cited.

- In one an eight-year-old girl who was noted to have vesicoureteral reflux (Figure 4), the underlying lesion was distal urethral stenosis which was diagnosed by urethral calibration. Urethral dilatation was performed following the diagnosis of reflux. Six months later a repeat x-ray study revealed no urinary reflux.

- In another case a four-and-a-half-year-old girl who had many upper urinary tract infections since age 1, was found to have double ureters on the right side (Figure 5) and right ureteral reflux. The slightly short tunnel on the right with a horseshoe orifice rather than a slit or stadium-like orifice was noted at cystoscopy. No outlet obstruction was present. Reflux was believed to be due to some deformity in Waldeyer's sheath, which is the supporting structure of the intramural segment of the ureter. This deformity is probably due to the anomalies in a double ureteral system.

Retrograde pyelograms with cystoscopy are important in selected patients. Cystoscopy and urethroscopy can easily rule out the presence of midurethral stenosis, urethral valves, meatal stenosis or bladder neck obstruction. Cystoscopy is also helpful in ruling out the presence of trabeculations

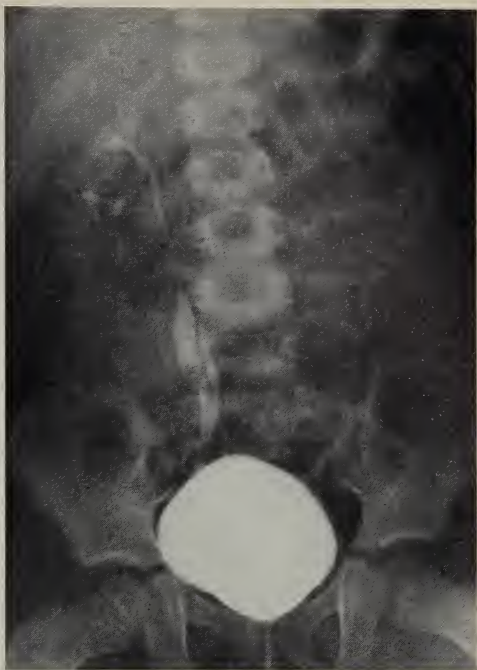


Figure 5.—Cystogram showing unilateral vesico-ureteral reflux associated with a reduplicated collecting system.

or diverticuli. Recently we have noted the association of certain types of ureteral orifices with reflux. A slit-like oblique orifice is normal. A horseshoe configuration is often associated with a short intramural ureteral segment. These short segments may encourage urinary reflux.

## Pediatrics

JOSEPH W. ST. GEME, JR., M.D.\*

I WISH to spend some time discussing the neonate. It is likely that the onset of pyelonephritis occurs in some patients at this very early age.

Carefully collected clean-voided urine cultures in newborn infants are difficult to interpret unless they are negative. False positive cultures (greater than 100,000 colonies per milliliter) may occur in almost one-third of newborn infants.<sup>61</sup> Thus, the technique of needle vesicopuncture has become extremely important and with practice one can obtain urines from the bladder in 90 percent of neonates. The dome of the bladder is readily ac-

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cessible in the pelvis of the newly born and it is frequently full, but one must be quick for it is not full for long. Urine specimens have been obtained in the neonate by stroking the vertebral column with the child poised over a sterile receptacle.<sup>62</sup> The Perez reflex is elicited, which involves a Moro-like response inductive of micturition. With good aim one may collect a satisfactory specimen of urine. This is a less predictable method of urine collection, so most clinics have employed the bladder puncture. In the toddler and older child, bladder puncture may be more difficult, although Saccharow and Pryles<sup>11</sup> recently reported that vesicopuncture was successfully performed on the first attempt in 92 percent of 500 children between 3 days and 11 years of age.

Using the technique of vesicopuncture, Nelson and Peters<sup>61</sup> reported that 8 percent of 25 male premature infants taken at random had more than 100,000 bacterial colonies per ml in their urine.

This is a surprising incidence of significant bacilluria and these studies should be repeated very carefully. Indeed, it seems to be evolving that "bladder" bacilluria in the range of 100 to 100,000 colonies per milliliter may be of pathogenic significance, whereas the same quantitative range of "clean-voided" or "catheter" bacilluria remains suspect or indeterminate.

Within the scope of neonatal urinary tract infections we have begun to learn about some new strains of *Escherichia coli*, called "pyelopathogenic" or "pyelonephritogenic" *E. coli* to be contrasted with enteropathogenic *E. coli*. Using the Kauffmann scheme<sup>63</sup> for serologic typing, the "O" serotypes which have been isolated from urinary tract infections most often are 01, 02, 04, 06, 07, 030 and 075. The serotype which has been found in most nursery epidemics is *E. coli* 04:H5.<sup>64,65</sup> The organism is a virulent, parenteral pathogen and produces pyelonephritis, bacteremia, and a cholestatic type of hepatitis and hyperbilirubinemia.<sup>66</sup> These infections have occurred in epidemics, much as enteropathogenic *E. coli* may cause epidemic gastroenteritis and sepsis in neonatal units. Balasanian and Wolinsky<sup>67</sup> looked very carefully at the source of mechanism of transmission of *E. coli* serotype 04:H5 in their neonatal unit. They documented the spread of the organism from infant to infant via the nurses' hands, but they were unable to determine the precise source. The organism was not isolated from the mothers, from nursery per-

sonnel, or from any of various physical sites in the nursery.

The very elegant work by Kunin and his group<sup>68,69</sup> spells out the story of asymptomatic urinary tract infection in the school age child. In this age group, approximately 1 percent of females and 0.04 percent of males yielded a significant number of bacteria (greater than 100,000 colonies per ml) in the urine. These studies included two to three positive cultures of midstream specimens before these youngsters were included as bacilluric. Only two of the 58 bacilluric girls in these studies were under the care of physicians because of obvious urinary tract infections. Thus, the majority were completely asymptomatic, apparently healthy children. However, 21 percent of these children had a past history of infection. Only 37 percent had pyuria. Subsequent study revealed an abnormal intravenous pyelogram in 20 percent and abnormal cystograph in 44 percent.

These facts urge us now to study the child at the time of the first urinary tract infection. Five or 10 years ago we would have waited for the second infection.

Another interesting statistic evolves from careful necropsy studies wherein one may detect histopathologic evidence of significant pyelonephritis in 2 percent of children.<sup>70</sup> This figure approximates the incidence of subtle bacilluria observed by Kunin and coworkers.

There are two other clinical situations in which the pediatrician should continue to search for obscure urinary tract infection. One is the fever of unknown origin. The other is chronic diarrhea. The yield may be no more than 1 percent but there can be no debate about the importance of detecting this small group of patients.

## Obstetrics and Gynecology

OFELIA T. MONZON, M.D.\*

DURING PREGNANCY, the prevalence of bacteriuria has been reported to be in the range of 2 to 10 percent. In indigent populations, an increase in the number of pregnant women showing positive urine cultures was noted by Turck and coworkers,<sup>71</sup> Monto and Rantz<sup>72</sup> and Henderson and associates.<sup>73</sup> Sick cell trait has also been shown by Whalley to be accompanied by an increase in the incidence of bacteriuria.<sup>74</sup> Bacteriuria during pregnancy was seen in 13.9 percent of women with

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sickle cell trait in contrast to 6.4 percent of Negro patients with normal hemoglobin. Conflicting reports, however, have been made with regard to the presence of bacteriuria and its relation to age and parity.

At the UCLA Center for the Health Sciences, a seven-year investigation of the incidence and course of bacteriuria during pregnancy revealed that 7.9 percent of women studied showed positive urine cultures during pregnancy. One-third of these patients manifested symptoms of urinary tract infection before delivery.<sup>7</sup> It should be noted at this point that a study conducted by Whalley and associates showed that 30 percent of pregnant patients admitted to hospital for pyelonephritis did not show significant bacteriuria at examination of their initial urine specimen.<sup>75</sup> Thus, treatment of all pregnant patients with known bacteriuria will not eliminate the appearance of antepartum pyelonephritis. Furthermore, our experiences have indicated that in about a third of asymptomatic patients bacteriuria will abate spontaneously without chemotherapy. These factors as well as the risk of the side effects of antibacterial therapy should be considered before using the more aggressive mode of continuous chemotherapy during pregnancy for eradication of bacteriuria as advocated by some investigators.

The relation of prematurity and bacteriuria has generated some controversial reports. Data reported by Kass<sup>4</sup> and other investigators indicated an increased prematurity rate in bacteriuric mothers. Our data<sup>7</sup> as well as those of Whalley,<sup>75</sup> Norden and Kilpatrick,<sup>76</sup> and Sleigh and associates<sup>77</sup> showed no difference in the prematurity rate of bacteriuric and nonbacteriuric women. The variation in findings could only be resolved by a well-controlled study with all possible variables taken into consideration.

The significance of bacteriuria persisting beyond the antepartum state has been studied by us and other investigators. We have recently reported on the effect of bacteriuria on renal function, the localization of the site of bacteriuria, and the demonstration of any underlying urinary tract disease in infected young females.<sup>78</sup> One-third of bacteriuric females studied had unilateral or bilateral renal involvement, as evidenced by bacteria in ureteral urine specimens, and either impaired urinary concentrating ability or pyelographic abnormalities. Symptoms and past history did not help us in localizing the site of infection. Vesico-

ureteral reflux was seen in a few patients with ureteral bacteriuria, one patient manifesting this abnormality after eight years of asymptomatic bladder bacteriuria intermittently controlled by therapy. The importance of careful bacteriologic studies and radiologic examinations in patients with persistent or recurrent bacteriuria cannot be overemphasized. In the absence of simpler methods of differentiating the site of infection in these patients, extensive urologic procedures such as those described by previous speakers may be indicated.

Finally, I would like to make an additional comment regarding the results of treatment in the above group of patients. In patients with renal bacteriuria and impaired urinary concentrating ability, improvement of renal function was noted following eradication of infection in those patients without radiographic changes of pyelonephritis. Further long range observations will be necessary to establish the ultimate significance of asymptomatic bacteriuria.

## Treatment

IRWIN ZIMENT, M.B., M.R.C.P.\*

THE FINDING of bacteriuria is always important, as it implies either active infection of the kidney or liability to subsequent infection.

When confronted with a urinary tract infection, one should always consider using sulfonamides, which are cheap and are usually well tolerated. If the infection is a recent one, and particularly if the patient is a female, the most common organism is *E. coli*, the vast majority of which are sensitive to sulfonamides.

Two other empirical means may be valuable in treating urinary infection, namely, acidification and large fluid intake. However, the value of acidification must take into consideration the type of antibacterial agent employed. Thus, sulfonamides are less soluble in acid urine, while streptomycin and kanamycin are far more active in an alkaline medium. Furthermore, attempts to acidify the urine may be unsuccessful if the infecting organism is a urease producer. Large fluid intake also has disadvantages when chemotherapy is being administered, since the urinary concentration of the drug will be reduced and the tissue concentration in the medulla affected. Thus, the traditional approach of giving a large fluid volume with acidifying agents

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will not necessarily be of benefit in the management of acute pyelonephritis, but is of value in preventing relapse once the infection has been controlled by chemotherapy, particularly when the infecting organism had rendered the urine alkaline.

In cases in which sulfonamide therapy is either unsuccessful or contraindicated because of allergic sensitivity, treatment with an antibiotic is required. The appropriate agent should, in general, be determined on the basis of bacterial susceptibility tests, and the least toxic drug should be selected. In most cases either ampicillin or tetracycline will be appropriate, but the presence of a resistant organism may necessitate the administration of a more toxic antibiotic. However, it should be noted that the combination of penicillin or ampicillin with a penicillinase resistant penicillin has a broad spectrum of activity against Gram-negative bacterial infections of the urine, and even *Pseudomonas* may be suppressed by this combination.<sup>79</sup> This approach to therapy is still experimental, but has been successful in my experience, although relapse is usual after the administration of drugs is discontinued. The combination may be useful in treating a less severe Gram-negative urinary tract infection in the presence of renal impairment where the hazard of employing a toxic antibiotic is not justified.

The therapy of pyelonephritis in the presence of renal insufficiency is often difficult since adequate concentrations of antibiotics in the urine may not be attained, and toxic complications are more likely to ensue. Where possible, an agent should be used which has no renal toxicity and little or no extra-renal toxicity. Antibiotics with these qualities include the penicillins, cephalothin, erythromycin and novobiocin, the latter being of some value against *Proteus*. Chloramphenicol is relatively safe in the presence of renal insufficiency, although there may be an increased danger of marrow depression. Streptomycin differs from the other aminoglycosides in that it is relatively free of nephrotoxicity, but vestibular damage has to be guarded against. The nephrotoxic agents kanamycin, gentamicin, the polymyxins and vancomycin can be used effectively in the presence of renal impairment if given in reduced dosage with careful monitoring of the patient for both renal and extrarenal toxicity. The whole subject of administration of antibiotics in the presence of renal insufficiency has been reviewed elsewhere and guides for appropriate dosage have been presented.<sup>80,81</sup>

Certain antibacterial agents in addition to the sulfonamides are of particular value in the treatment of urinary tract infections, although of no value for extra-renal infections or in the presence of renal insufficiency. Nitrofurantoin is the most popular of these "urinary antiseptics," and although it has a wide spectrum and may be effective in pyelonephritis, it is relatively expensive and it may cause nausea and other toxic effects which limit its use. Nalidixic acid may be of similar value, but organisms tend to develop resistance during therapy, so that the drug is suitable for only short courses of treatment. Methenamine mandelate (Mandelamine®) is very effective in the presence of a urinary pH of less than 5.5, and effective acidifying agents must be given with the drug with frequent testing of the urine to ensure that the pH is appropriately lowered. Such therapy may be of particular value for long-term sterilization of the urinary tract.

The length of the course of antibacterial therapy in pyelonephritis is a matter of controversy.<sup>82,83</sup> The initial course should be 10 to 14 days, at least, with more prolonged therapy in cases of relapse or recurrent infection. Very long-term therapy will be needed in more resistant cases, and the appropriate drug should be determined by frequent urine cultures. If therapy is required for several months, it is preferable to use different agents for periods of a few weeks successively.

## Comments

LUCIEN B. GUZE, M.D.

SOME OBSERVERS have raised questions about the role of bacteria in the pathogenesis of chronic pyelonephritis. In instances where urine or renal biopsy culture or both have been negative, in the presence of histologic disease, the etiological significance of bacteria has been depreciated. In these circumstances, other possible causes of disease have been postulated. Evidence is available which suggests that these alternate hypotheses may not be correct. Pertinent data have been derived from experimental and clinical observations and may be summarized as follows: After the production of acute pyelonephritis in rats with either *Bacillus proteus*<sup>52,54,84</sup> or *E. coli*,<sup>85</sup> infection subsided and ultimately bacteria were no longer recovered from renal cultures or urine. However, if one examined the residual scars with fluorescent antibody technique, it was regularly possible to demonstrate persistence of bacterial antigen. Thus,



if these animals had been examined only at the stage of disease at which there was renal scarring with negative cultures, it might have been assumed that bacteria played no role. Fluorescent antibody studies indicated, at least, that there had been infection at some previous time. Clinical confirmation of this has been obtained by the recent studies of Aoki and associates.<sup>86</sup> These investigators used fluorescent techniques and antiserum to an antigen shared by most strains of Enterobacteriaceae. Bacterial antigen could not be detected in any of the kidneys obtained from 20 controls nor was antigen found in eight of nine kidneys from patients with chronic renal disease other than pyelonephritis. Large quantities of antigen were detected in seven of eight patients with classical bacterial pyelonephritis. Of great importance was the fact that antigen was detected in seven of eight patients with "abacterial" pyelonephritis who had sterile urine cultures and who denied any history of urinary tract infection. These findings indicated that negative urine cultures and absence of history are insufficient to exclude previous renal infection. The investigators interpreted the data as suggesting that "bacterial infection may be the initiating factor in many cases of so-called 'abacterial' pyelonephritis."

An hypothesis might be developed to explain the progression of chronic pyelonephritis in the absence of viable bacteria. Speculation might be made that this occurs as the result of autoimmune disease which was initiated by the active bacterial infection and continues in the presence of persistent bacterial antigen. Very preliminary data from our laboratory may be of interest in this regard.<sup>55</sup> In order to see if autoimmunity occurred in experimental pyelonephritis, highly inbred Fisher rats were infected intravenously with *Streptococcus faecalis* which produces an active pyelonephritis closely mimicking the disease in man.<sup>50</sup> After 8 weeks of infection, lymphocytes from infected animals were transferred to noninfected, immune-tolerant Fisher rats (appropriate controls transferring lymphocytes from noninfected donors were included). At suitable intervals, the recipients were sacrificed and kidneys examined. Distal tubular lesions were produced in kidneys of animals receiving lymphocytes from infected donors. These lesions were not noted in animals which received lymphocytes from uninfected donors. Two days after transfer, lymphocytes were collected around basement membranes of distal tubules and were

accompanied by vigorous cytotoxic and cytolytic reactions. Vacuolization developing between basement membranes and epithelium of distal convolutions collecting ducts and renal pelvis was a major mechanism of cell damage. Repair was evident within 5 days and was quickly completed in the collecting ducts and pelvic epithelium, but degeneration and regeneration continued in the distal convoluted tubules for at least 7 weeks. In animals with enterococcal pyelonephritis, comparable distal tubular lesions were not found until 6 weeks after infection. Thus, it appeared possible to transfer, via lymphocytes, a component of renal damage found in pyelonephritis. Whether or not other histologic features could be similarly transferred by using lymphocytes from animals infected longer than eight weeks remains to be demonstrated. Also, it will be important to determine if similar immune mechanisms are operative in man. It is intriguing to speculate that progression of pyelonephritis may be immune in nature and may require immunosuppressive therapy instead of, or in conjunction with, antimicrobial medication.

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## MEDICAL STAFF CONFERENCE

# The Prader-Willi Syndrome

*These discussions are selected from the weekly staff conferences in the Department of Medicine, University of California Medical Center, San Francisco. Taken from transcriptions, they are prepared by Drs. Martin J. Cline and Hibbard E. Williams, Associate Professors of Medicine, under the direction of Dr. Lloyd H. Smith, Jr., Professor of Medicine and Chairman of the Department of Medicine.*

DR. SMITH:\* We have an interesting “paraendocrinologic” problem for presentation this morning. The case summary will be given by Dr. Homer Boushey.

DR. BOUSHEY:† The patient (Figure 1) is a 21-year-old Mexican-American male who first came to the surgical clinic in 1965 for correction of a left inguinal hernia and undescended testes. He was the eighth child born to a 41-year-old mother who had attempted to induce abortion with an unknown medication at two months’ gestation. The attempt produced vaginal bleeding but not expulsion of the fetus. Fetal movements were decreased throughout gestation. Delivery was normal at term. The patient’s birth weight was 4 pounds, 8 ounces. His siblings weighed between 7 and 8 pounds at birth. The patient’s mother recalls that he was blue for the first three days of life and could not suck, gaining little weight in the first month. At age one month, he was admitted to the San Francisco General Hospital and stayed there for 30 days. Weight gain remained slow.

The patient’s development was slow. There was little spontaneous movement for the first six months of life. He sat at one year, walked and talked at two and a half years, and was not toilet trained until five years of age. From the age of nine months to 13 years he had a number of grand mal seizures, which were poorly controlled with anti-convulsant medications. Since age 13 he has had no seizures, despite the withdrawal of anticonvulsant therapy. Intellectual growth has been impaired despite special schooling. He remains unable to

read or write, and the full-scale intelligence quotient has been measured at 59. The patient’s social adjustment, however, is apparently very sound. Although he was always short in stature, his weight was apparently appropriate for his height after the first year of life. At age 11 he started to gain weight rapidly. There is no persistent hyperphagia.

Medical history includes an operation for correction of right internal strabismus at age 8 and



Figure 1.—Patient with Prader-Willi syndrome presented at this conference.

\*Lloyd H. Smith, Jr., Professor and Chairman, Department of Medicine.

†Homer A. Boushey, M.D., Intern in Medicine.



multiple dental extractions at age 11 because of caries and malocclusion. At age 17 the height was 151 cm ( $-3$  standard deviations for age) and the weight was 61.6 kg (falling within the mean for chronologic age and  $+3$  standard deviations for height age). The patient's facies was characterized by close-set slit-like eyes, a beaked nose, low-set ears and a fish-like mouth with a high arched palate. There was some facial asymmetry, the right side being smaller than the left. Examination of the eyes showed slight ptosis of the right eyelid in addition to right esotropia and amblyopia exanopsia. The patient's habitus was generally feminine with subcutaneous fat distribution over the breasts and hips. The hands were small, described as elfin, with long, thin, delicate fingers. Examination of the genitalia revealed a small, uncircumcised penis with hypospadias; partially descended, small left testicle; and undescended right testicle. A left inguinal hernia was found. Neurologic examination revealed generalized hypotonia but was otherwise unremarkable. Because of these findings, the patient was referred to the metabolic service before corrective operation.

Evaluation on the metabolic ward included roentgenographic studies revealing a sella turcica decidedly decreased in its anterior-posterior diameter but wider than normal in its lateral dimensions. The bone age was determined as  $15\frac{1}{2}$  years (the chronologic age then was 18 years). Buccal smear showed a male pattern. The karyotype pattern was normal for a male, but an abnormal chromatin clump of uncertain significance was found in approximately half the cells. Muscle biopsy was normal by light microscopy, but electromyographic studies showed abnormal myopathic potentials. The protein-bound iodine level was 5.0 micrograms per 100 ml. Radioactive iodine uptake was 11 percent at 24 hours, but the thyroid responded promptly to thyroid-stimulating hormone. Urine gonadotropins were positive at 5.0 and negative at 80 mouse units. 17-Hydroxy and 17-ketosteroids showed a normal basal excretion, and they responded appropriately to adrenocorticotrophic hormone and metapyrone administration. Testosterone levels were decidedly diminished at 3.3 micrograms per 24 hours (normal level for females, 5.0 to 20; for males, greater than 100). Response to arginine infusion was poor, with only a slight rise in serum growth hormone level (from a fasting level of 0.5 millimicrograms per ml to a peak level of 2.9 millimicrograms per ml at 30

minutes). An electroencephalogram showed diffuse slowing throughout. An electrocardiogram revealed early right ventricular hypertrophy which was confirmed by vectorcardiography. Prothrombin time, creatinine, phosphokinase, and alkaline phosphatase levels were within normal limits. The patient was referred to the urologic service for left orchipexy, inguinal hernia repair, and testicular biopsy. The biopsy specimen showed no evidence of spermatogenesis; the seminiferous tubules were lined only by Sertoli cells.

After discharge, the patient was seen once again in clinic for an effusion of the left knee. No cause could be found and the effusion resolved spontaneously.

Four days before the patient's second admission, a productive cough and fever developed, for which he was given tetracycline and a cough medication. He became lethargic and weak and was brought to the emergency room where an x-ray film of the chest showed left lower lobe pneumonia. The blood sugar level measured 1,450 mg per 100 ml with a serum osmolality of 445 milliosmols per liter. The patient was not acidotic, and initially there was no acetonuria. A diagnosis of hyperosmotic, nonketotic, diabetic precoma was made, and treatment with intravenous fluid, insulin, and antibiotics was followed by prompt clinical improvement. With this improvement, it was possible to evaluate further the patient's pituitary function. Arginine and insulin infusions (Table 1) showed blunted growth hormone responses. A glucose tolerance test performed two weeks after recovery was decidedly abnormal and revealed a diminished insulin reserve (Chart 1). Following recovery the patient was discharged with no antidiabetic medications.

DR. SMITH: Thank you very much, Dr. Boushey. Perhaps we can see the films now, Dr. Sheft.

DR. SHEFT: \* Our radiographic studies date back to 1966. At that time a film taken for skeletal age shows that the distal radial epiphyses, several of the metacarpal epiphyses, and the proximal phalangeal epiphyses are all open. This is quite abnormal in an 18-year-old male and reflects a bone age of approximately  $15\frac{1}{2}$  years. Notice the configuration of the fingers—very thin and very long. Although patients with the Prader-Willi syndrome sometimes have clinodactyly and syndactyly, this patient has neither of these findings.

\*Douglas J. Sheft, M.D., Assistant Professor of Radiology.

TABLE 1.—Results of Arginine and Insulin Tolerance Tests in Patient Presented

Arginine Tolerance Test (30 grams given intravenously over 30 minute period)

	Test 1	Test 2	Test 3	Test 4
Time (minutes)	0	30	60	90
Blood glucose (mg per 100 ml)	164	178	174	148
Plasma growth hormone (millimicrograms per ml)	<1	7.1	5.3	4.0
Plasma insulin (microunits per ml)	<5	21	24	14.5

Insulin Tolerance Test (0.2 units per kg body weight given intravenously)

	Test 1	Test 2	Test 3	Test 4
Time (minutes)	0	30	60	90
Blood glucose (mg per 100 ml)	165	64	37	94
Plasma growth hormone (millimicrograms per ml)	1.0	...	6.8	6.0

TABLE 2.—The Prader-Willi Syndrome:  
Original Description<sup>1</sup>

Extreme hypotonia in the newborn period without complete loss of the deep tendon reflexes.  
 Gradual improvement of the hypotonia during infancy and severe developmental delay.  
 Dwarfism with retarded bone age and generalized obesity by school age.  
 Cryptorchidism with flat hypoplastic scrotum and poor development of secondary sexual characteristics in boys.  
 Development of diabetes mellitus in older patients.

Skull examination demonstrates an extremely small sella turcica and abnormal dentition. He has no teeth in his maxillary arch and several teeth remaining in his mandibular arch. The skull is rather short and brachycephalic, but the proportion between the face and the calvarium is normal. The posterior-anterior film of the skull reflects the narrowed orbits which Dr. Boushey described on physical examination. The bone density is normal.

A representative film of the patient's extremities suggests that there is pronounced muscle wasting. The bones are quite narrow; their maturation is delayed. Knee examination in 1966 showed a synovial effusion with distension of the suprapatella bursa. Also at that time the patient had some manifestations of arthritis in the hips.

DR. SMITH: We have asked Dr. Dennis M. Bier to open discussion concerning this unusual problem in paraendocrinology and metabolism. Dr. Bier is a graduate of the New Jersey College of Medicine and received his internship and residency training in pediatrics at the University of California Medical Center, San Francisco. He is currently a Research Fellow in the Cardiovascular Research Institute and in Pediatrics. Dr. Bier has been interested in this disorder and will begin by describing what is known about the syndrome.

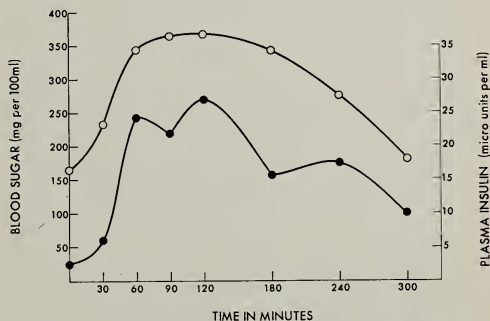


Chart 1.—Oral glucose tolerance test with simultaneous blood glucose and plasma insulin determinations in patient presented. 100 grams of glucose administered. ○ = blood sugar levels. ● = plasma insulin levels.

DR. BIER: This patient probably represents an example of the syndrome which was first described in 1956 by Prader, Labhart, Willi, and Fanconi<sup>1</sup> at the Eighth International Congress of Pediatrics. Not all the features in this patient, however, are absolutely typical.

Prader and his colleagues described ten patients with similar clinical features (Table 2). Their original summation presents the major features of the syndrome. Approximately 125 patients were described or mentioned, and 13 years later their outline still represents essentially all that is known about the syndrome. In addition to the strong facial similarity between the patients, all had severe neonatal hypotonia, hypogonadism, dwarfism, mental retardation, and obesity. None of the features is diagnostic or unique in its own right, but the full complement of features appears to be distinctive enough to constitute a true clinical syndrome. It is likely that this syndrome is much more common than its description in the literature would indicate.

The sex distribution has been almost 3:1 males to females, but this may be only a reflection of the

TABLE 3.—*The Prader-Willi Syndrome: Prenatal Features*

Family history
Two patients with twins
A brother and sister with the syndrome
Parents of one case are cousins
DIMINISHED TO ABSENT INTRAUTERINE MOVEMENTS (42/50)*
Gestational bleeding
Length of gestation
TERM (51/77)
Longer than 40 weeks (19/77)
Less than 38 weeks (7/77)
Type of delivery
13 Breech
6 Caesarean section
BIRTH WEIGHT BELOW THE MEAN
20 Patients with intrauterine growth retardation

\*The first number in parentheses indicates the number of patients exhibiting a particular feature. The second number indicates the number of patients in which the feature is mentioned in case history.

TABLE 4.—*The Prader-Willi Syndrome: Clinical Features During the Newborn Period*

Anoxia
MARKED HYPOTONIA
ABSENCE OF SPONTANEOUS ACTIVITY
WEAK TO ABSENT CRY
POOR SUCK AND SWALLOW
HYPOGONADISM
CRYPTORCHIDISM
FLAT HYPOPLASTIC SCROTUM
Thermoregulatory lability

ease with which hypogonadism can be detected in boys. The clinical course can be divided into a number of phases which are listed in the next few tables. Features which have been so characteristic as to represent major manifestations of the syndrome appear in capital letters in the tables.

The family history (Table 3) is generally unremarkable. Two patients have had twin siblings. In the first case<sup>2</sup> the other twin was normal but "small." In the second case, one of our own series, the other twin died *in utero* approximately five days before delivery. Two other patients have come from the same family and another patient's parents were cousins.<sup>3</sup> However, the siblings had unusual clinical features, and the patient of the consanguineous parents did not have the prominent neonatal hypotonia which is one of the major manifestations of the syndrome.

The most characteristic feature of the gestational history (Table 3) is diminished intrauterine movements. This finding has led to the belief that the syndrome is, therefore, not related to those

TABLE 5.—*The Prader-Willi Syndrome: Clinical Features During Childhood*

History
DEVELOPMENTAL RETARDATION
Intelligence quotient 11 to 90
Seizures or loss of consciousness
Abnormal electroencephalogram (24/63)*
SLOW IMPROVEMENT IN HYPOTONIA ACTIVITY EATING
ONSET OF OBESITY (usually age 2 to 4 years)
HYPERPHAGIA
Rage reactions
Physical Characteristics
FACIES
FISH MOUTH
UPTURNED NOSE
ALMOND-SHAPED EYES WITH MONGOLOID SLANT
Herniae
Scoliosis
Strabismus
ACROMICRIA
Genu valgum
Microcephaly
HYPOGONADISM
SHORT STATURE
Small mandible
Dislocated hips
Acanthosis nigricans
Malocclusion and/or caries

\*The first number in parenthesis indicates the number of patients exhibiting abnormal electroencephalogram. The second number indicates the number of patients in which abnormal electroencephalogram is mentioned in case history.

events that surround labor and delivery but is determined by some genetic factor or intrauterine insult. This hypothesis receives some support from the fact that the birth weights of children with the Prader-Willi syndrome are slightly below the mean birth weights of normal children of the same gestational age. Approximately 20 patients have had definite intrauterine growth retardation, with birth weights below the tenth percentile for gestational age. The length of gestation is usually normal, but 19 of the children have been carried longer than 40 weeks. Some of the mothers have had bleeding during pregnancy, and approximately 10 percent of the children were breech presentations.

At least 30 of these patients have had a definite history of birth anoxia (Table 4) which may complicate the diagnosis in early infancy. Most prominent in the newborn period is severe hypotonia with absence of spontaneous activity. In addition, because of their extremely poor suck and swallow, many have to be force-fed or fed by gavage for prolonged periods. One child was fed by gavage<sup>2</sup> and another by dropper<sup>4</sup> for the first five months of life. Also noticeable in the boys at birth is the small penis and flat, empty scrotum. An additional group





Figure 2.—Seven and one-half year-old boy with the Prader-Willi syndrome.

of infants have had some difficulty maintaining a stable body temperature.

In childhood (Table 5) there is gradual improvement in the hypotonia and feeding, but some hypotonia persists into adult life. In addition, these children have developmental retardation in all spheres. Most do not sit until they are one year old, do not walk until they are two, and do not talk until they are more than two years old. One patient never learned to walk<sup>5</sup> and another has not learned to talk.<sup>6</sup> The intelligence quotient estimates in later life have ranged from 11 to 90, but most of the children have quotients between 40 and 60.

Usually between the ages of one and four years obesity becomes apparent and is often accompanied by hyperphagia. Some parents have been forced to lock up food at home, and the children have been known to eat almost anything, including garbage. One child ate the cattle food on the farm where he lived.<sup>7</sup> Some patients also have periodic rage reactions, often related to having their desires for food thwarted.

A few children, including the patient today, have

TABLE 6.—*The Prader-Willi Syndrome: Clinical Features During Adolescence*

Boys	
DELAYED PUBERTY WITH POOR EXPRESSION	
INFERTILITY	
Girls	
GENITALIA USUALLY NORMAL	
Puberty and menses delayed in some	
Diabetes Mellitus	Number of Patients
Overt	10
Normal (test not specified)	10
Chemical diabetes (test not specified)	4
Normal oral glucose tolerance test only	24
Normal cortisone glucose tolerance test	15
Positive oral or cortisone glucose tolerance test	18
Total 81	

had seizures or episodes of unconsciousness during childhood, but these episodes have not persisted into adult life. Electroencephalographic studies have demonstrated multiple different dysrhythmias in 24 of 63 tracings.

Usually these children are short, although not severely dwarfed, and appear at the lower end of the normal scale. The facies is quite characteristic, featuring almond-shaped eyes having a Mongoloid slant, upturned nose, and a "fish-shaped," triangular upper lip. The hypogonadism found at birth remains, and two-thirds of the boys have bilateral cryptorchidism. The remaining boys usually have small testes located in the inguinal canals, and the scrotum remains flat and empty. Only two of the girls have had small external genitalia.<sup>8,9</sup> One of the most characteristic physical findings, felt by some investigators to be absolutely necessary for the diagnosis, is very small hands and feet with tapering fingers and toes. The patient presented today does not have true acromicria because he lacks the tapering, however, his hand abnormality has been described in some patients.

Strabismus, genu valgum, small mandible, and dental caries with malocclusion or enamel hypoplasia are among the more frequently associated features. Less common physical findings associated with this syndrome have included microcephaly, scoliosis, dislocated hips, inguinal herniae, and acanthosis nigricans.<sup>8,10,11</sup> This last feature is interesting because it is associated with a number of neuroendocrinopathies.

Many of these clinical features are demonstrated in Figure 2. This patient, a 7½-year-old boy, demonstrates the obesity, the slightly short stature and the characteristic facies. In addition he has right strabismus and genu valgum.

In adolescence (Table 6) the boys generally have diminished and delayed puberty with decreased secondary sex characteristics. Testicular biopsy in six postpubertal men, including the patient in present case, demonstrated atrophy or absence of spermatogenesis.<sup>10,12,13</sup> In one prepubertal boy,<sup>14</sup> no testis was found at herniorrhaphy. Three other prepubertal biopsy specimens were normal for the patient's age.<sup>14,15,16</sup> Another specimen showed very few spermatogonia and an absence of Leydig cells.<sup>17</sup> There has been no constant disorder in sexual maturation in the girls. One girl menstruated only once.<sup>18</sup>

Disorders of carbohydrate intolerance are usually discovered during adolescence or early adult life (Table 6). About 39 percent of those tested had a negative oral glucose tolerance test only, and 12 percent were described as having no diabetes, although the test procedures were not mentioned. No insulin measurements were made during these tolerance tests except in the patient presented today, who had a low insulin response to glucose. Dunn<sup>19</sup> determined plasma insulin levels after an oral glucose load of 1 gram per kg body weight in five of his patients. One of these patients, who had a diabetic response during a standard oral glucose tolerance test, had elevated insulin levels at one and two hours when compared with the normal control subjects. Fasting insulin levels in nine patients were within normal limits.<sup>18,19,20</sup> Despite the fact that diabetes occurs at a young age, it is characteristically non-ketotic and non-insulin dependent, resembling maturity-onset diabetes and responding well to oral hypoglycemic agents. The patient presented today has required neither insulin nor oral medications since his last hospital admission.

The prognosis in adult life is uncertain. The oldest living patient reported in the literature was 43 years old in 1966.<sup>20</sup> He had overt diabetes and an episode of diabetic gangrene of a toe. There is no further follow-up on this patient in the literature. Prader's oldest patient died at the age of 28 of renal failure, secondary to diabetic nephropathy, and resultant pulmonary edema. Recently Steiner<sup>12</sup> published the autopsy findings on this patient, as well as the postmortem results of another patient who died at 23 years of age and who had had chemical diabetes since age 19. The former patient had severe arteriosclerosis and glomerulosclerosis. There was an absence of glycogen in the liver and the myocardium. The latter patient died as a result of multiple pulmonary emboli. Both patients

had persistence of the thymus and para-aminosalicylic acid-positive, homogeneous lesions of the capillaries, as well as an increased number of mast cells. Examination of the pituitary gland and brain in both cases revealed no significant abnormalities.

Necropsy was done in three other cases. One 42-year-old man<sup>10</sup> developed congestive heart failure and died suddenly. There was pulmonary edema and emboli in addition to an old myocardial infarction. The typical pathology of diabetes was found in the pancreas and kidneys. There is no mention of the thymus. In the pituitary, there was a "focal preponderance of chromophobes, suggesting chromophobe adenoma." No obvious hypothalamic lesion is mentioned. The two other patients who died were children.<sup>9,21</sup> Both were thought to have had cardiorespiratory syndrome of obesity. At autopsy, both patients had pulmonary edema, one had pneumonitis, and one had fatty infiltration of the myocardium. The brains in both children were also normal. The fact that the pituitary-hypothalamic structures were essentially normal in four of the five patients who died is important in view of the possible causes of this syndrome.

Laboratory investigations have not been helpful in establishing either the diagnosis or the cause of this syndrome. All routine hematologic studies, blood chemistries, and muscle enzymes have been normal. Lipid panels have been normal in the 40 patients tested. Skull x-rays are generally normal, but some patients show variations in skull shape (dolichocephaly, brachycephaly, turriccephaly) or have a small sella turcica. The bone age is retarded in approximately 55 percent (39 of 71 patients). Pneumoencephalograms in 6 of 12 patients showed varying degrees of ventricular dilatation or cortical atrophy. Chromosome analyses were performed in 70 patients; 60 were normal. Two patients were possibly abnormal.<sup>22,23</sup> The remaining eight patients showed different patterns, including three patients with elongated Y chromosomes,<sup>11,19</sup> an XYY karyotype,<sup>19</sup> a balanced 14/18 translocation,<sup>24</sup> a 13/15 translocation,<sup>17</sup> a mosaic 13/15 trisomy,<sup>22</sup> and the patient today, who had an unusual chromatin body in 50 percent of the cells.

The electromyogram was normal in almost all instances with non-diagnostic findings in the others. Nerve conduction has been normal. Muscle biopsy has been normal in most patients. In one patient the findings were consistent with neurogenic atrophy,<sup>25</sup> and another patient showed finely beaded nerve fibers in the smaller bundles.<sup>18</sup>

TABLE 7.—The Prader-Willi Syndrome:  
Differential Diagnosis

	Syndrome			
	Prader-Willi	Laurence-Moon-Biedl	Froelich	Lynch and Coworkers <sup>22</sup>
Obesity	+	+	+	0
Hypogonadism	+	+	+	+
Mental Retardation	+	+	0	0
Dwarfism	+	0	+	+
Diabetes Mellitus	+	±	0	+
Diabetes Insipidus	0	+	+	0
Retinitis Pigmentosa	0	+	0	0
Family	0	+	0	+
Other	Hypotonia	Polydactyly	Central nervous system signs	Hyperlipemia

Urinary 17-ketosteroid and 17-hydroxycorticoid levels, including responses to the administration of adrenocorticotrophic hormone and metapyrone, have been normal in general, although three patients did not show a satisfactory response to corticotropin or metapyrone.<sup>6,8,17</sup> Urinary gonadotropins have shown both high and low values. Growth hormone levels in five of Dunn's patients<sup>19</sup> and in the patient today were normal.

The major differential diagnosis of the Prader-Willi syndrome (after the infantile hypotonic period) is shown in Table 7. Although the Laurence-Moon-Biedl syndrome is associated with obesity, hypogonadism, mental retardation and, occasionally, diabetes mellitus, it is easily distinguished from Prader-Willi syndrome by its familial nature, the absence of dwarfism and infantile hypotonia, and the presence of retinitis pigmentosa, digital abnormalities, and dia-

betes insipidus. Froelich's syndrome, which is caused by lesions that produce hypothalamic destruction (usually craniopharyngiomas) is characterized by obesity, dwarfism, and hypogonadism. There is no mental retardation, infantile hypotonia or diabetes mellitus, however, and the obesity can start at any age. These patients, as originally described by Froelich, have signs of increased intracranial pressure with headache, vomiting and papilledema. In 1966, Lynch, Kaplan, Henn, and Krush<sup>26</sup> described a familial disease with hypogonadism, diabetes mellitus, and dwarfism. These children, however, were not obese and had no mental retardation. In addition, they had hyperlipemia and diabetes of the juvenile variety. A number of authors have suggested that the combination of severe infantile hypotonia and hypogonadism is so characteristic of the Prader-Willi syndrome that the diagnosis can be made before the onset of obesity and hyperphagia. Schneider and Zellweger<sup>27</sup> followed two infants with the characteristic facies and hypogonadism, who did not have obesity by four and six years of age respectively, and who were thus classified as *forme frustes* of the Prader-Willi syndrome. Today's patient resembles these children in that he apparently was of normal weight for his size until 11 years of age.

With regard to etiology, it is generally felt that gross chromosomal defect or birth injury can be excluded for reasons obvious from the previous discussions. Other possible explanations include some prenatal, physical, or chemical insult to the hypothalamic regulatory system; or a genetic, inherited metabolic defect. Both of these possibilities have counterparts in animals (Table 8).

The prototypes of hypothalamic injury are mice treated with gold thioglucose, which destroys the ventromedial nuclei of the hypothalamus, the so-called satiety centers. These mice are obese, hyper-

TABLE 8.—The Prader-Willi Syndrome: Suggested Pathogenic Mechanisms

Experimental Model	Characteristics of Model						
	Obese	Hyperglycemic	Hyperlipemic	Fertile	Fasting Lipogenesis	Fed Lipogenesis	Mobilization
Hypothalamic regulatory disturbance <sup>28</sup> (gold thioglucose mice)	+	0	+	±	0	+	+
Inherited metabolic disorder <sup>28</sup> (obese-hyperglycemic mice)	+	+	+	0	+	+	0
Prader-Willi ( <i>in vitro</i> ) <sup>13</sup>	—	0	0	—	+	—	0
Prader-Willi ( <i>in vivo</i> ) <sup>23</sup>	+	±	0	0	—	—	+



lipemic, and hyperphagic, but are not hyperglycemic. In addition, they have normal lipogenesis and can mobilize fatty acids from adipose tissue when hormone sensitive lipase is activated by catecholamines.<sup>28</sup> As was previously mentioned, however, patients with the Prader-Willi syndrome who have been studied at postmortem examination have had no obvious hypothalamic injury. An inherited metabolic defect might be similar to that of the obese-hyperglycemic mice. In the homozygous recessive state, these mice are, as their name implies, both obese and hyperglycemic in addition to being infertile and hyperlipemic.<sup>28</sup> These animals may have abnormal lipogenesis during fasting and poor mobilization of fatty acids from adipose tissue after stimulation of lipolysis with catecholamines.

The latter hypothesis has been advanced by Johnsen,<sup>13</sup> who presented *in vitro* studies with adipose tissue obtained from seven children with the Prader-Willi syndrome. The adipose tissue biopsy specimens "showed elevated palmitoleic acid levels suggestive of hyperlipogenesis." Also, "fat synthesis from acetate during fasting was tenfold greater than in tissue from unaffected sibs and hormone stimulated lipolysis was depressed." None of Johnsen's patients, however, were diabetic or hyperlipemic as are the obese-hyperglycemic mice. Further doubt has been cast on the specificity of Johnsen's hypothesis by Knittle's<sup>29</sup> recent demonstration that epinephrine-stimulated lipolysis in adipose tissue of obese children was decidedly decreased when compared with that of non-obese children. Thus, the poor hormone-stimulated lipolysis observed by Johnsen is not a specific pathogenic mechanism for the Prader-Willi obesity. In addition, preliminary results of our *in vivo* studies in six patients with this syndrome (four patients of our own and two of Doctors Sugarman and Boder) indicate that adults and children with the Prader-Willi syndrome have a normal rise in free fatty acids in plasma during a continuous norepinephrine infusion. Deficient lipolysis, therefore, does not seem to be present *in vivo*.

Finally, some observers have proposed a third etiologic possibility—that of an insulin antagonist similar to the one described by Vallance-Owen.<sup>30,31</sup> This synalbumin antagonist causes decreased incorporation of glucose into muscle but facilitates incorporation of glucose into adipose tissue. Significant insulin antagonism was demonstrated in one of six patients in Dunn's series.<sup>19</sup> That patient,

a boy, was not diabetic and one of his brothers also showed the antagonist. Approximately 20 to 25 percent of the population is estimated to have this antagonist,<sup>32</sup> and its significance in the Prader-Willi syndrome is uncertain.

DR. SMITH: Thank you very much, Dr. Bier. We have time for comments or questions concerning this particular patient and this strange entity. Dr. Havel, do you have anything to add? Is this a lipid disorder?

DR. HAVEL: \* I have really nothing to add to the excellent clinical description presented by Dr. Bier. I would like to congratulate Dr. Smith, who made the diagnosis in the patient presented today. This boy was studied in the Clinical Research Center two years ago and no diagnosis was established. Then the patient entered with hyperosmolar coma and was presented to Dr. Smith on ward rounds. He consulted the medical literature, and the diagnosis rapidly became apparent to him.

Dr. Bier and I have become interested in this syndrome and are studying a number of patients in the Pediatric Clinical Research Center. We are mainly interested in whether these patients have defective fat mobilization upon stimulation of hormone-sensitive lipase. We would also like to know about other aspects of the regulation of fat mobilization in these patients with respect to their tendency to accumulate adipose tissue.

In some respects, the reason I originally developed an interest in the Prader-Willi syndrome was related to my interest in total lipodystrophy. In many ways the clinical problems of these patients appear to be a mirror image of those presented in the Prader-Willi syndrome. Patients with lipodystrophy are not hypotonic; in fact, they are very muscular. Also, they have virtually no adipose tissue. Both conditions, however, have certain other features in common: The patients are mentally retarded, and they often present other suggestions of an endocrinopathy-acanthosis nigricans, for example. Patients with lipodystrophy have excessive fat mobilization in relation to their very small adipose tissue mass, and they may have a defect in the hypothalamus. We have wondered if some opposite defect might exist to account for some of the features of the Prader-Willi syndrome.

DR. SMITH: Thank you very much, Dr. Havel. I can assure you that this patient was presented to me

\*Richard J. Havel, M.D., Associate Director of the Cardiovascular Research Institute and Professor of Medicine.

on ward rounds as a case of non-ketotic, hyperosmolar precoma in a diabetic, but I certainly did not know what the entire phenomenon represented. I only know that this entity was something quite different from anything I had ever seen, and I began a frantic thumbing of the literature. This patient is the first I have had occasion to see with this syndrome.

DR. CLINE: \* What is the significance of Barr bodies in 50 percent of the cells with normal karyotypes?

DR. BIER: There were no Barr bodies, but some unidentified mass that stained with the characteristics of chromatin and was felt, possibly, to be an additional chromatin "dot." The karyotype will be repeated, I suspect, when the patient returns.

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## A Coronary Care Unit in a 25-Bed Rural Hospital

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CORONARY CARE UNITS have proliferated in California as well as throughout the country in the last 3 years. It has been well demonstrated that intensive care of the monitored patient with myocardial infarction can reduce the mortality by about one-third, primarily by aggressive treatment of serious arrhythmias and early treatment of minor arrhythmias to prevent cardiac arrest.

Much has been published about coronary care units in larger hospitals, but little is available concerning extension of this facility to small community hospitals. It is believed that the coronary care unit described in this article is the first in so small a hospital. The purpose of this article is to highlight some of the problems peculiar to a small hospital in a rural community.

The California Heart Association has urgently recommended development of a coronary care facility in any hospital receiving patients with myocardial infarction.<sup>1</sup> As it is well known that the mortality rate from acute myocardial infarction is highest in the first hour after onset, patients are poorly suited to transportation to a larger medical center a considerable distance away.

### Initial Problems

Many questions were immediately raised when the 25-bed Mount Shasta Community Hospital,\*

serving a population of about 18,000 people in southern Siskiyou County, started plans for a coronary care unit. The most crucial initial questions included the following:

1. How does one go about obtaining the necessary information to organize a coronary care unit, design the physical plant, assemble the equipment, train personnel and operate the unit?
2. Can enough nurses, already scarce in a rural area, be motivated and trained in the techniques of intensive coronary care?
3. Can physicians in general practice develop the skills to initiate and operate a coronary care unit?
4. Can the cost of such a facility be kept within feasible limits?
5. Does the expected patient volume of patients with acute coronary disease justify the expense involved, as well as the loss of beds to general care, if modification to the existing hospital plant is undertaken instead of new construction?

### Background

Fortunately, the answers to these questions were fairly easily supplied. Extensive help was given by internists from neighboring communities and by the California Heart Association. Several publications were helpful.<sup>1-6</sup> Regional Medical Programs provided consultative services of an electrical engineer which were essential for proper wiring of the unit. The recent publication by the California Heart Association on Coronary Care Units (1969)<sup>7</sup> consolidates much helpful reference material.

Submitted 3 April 1969.

Reprint requests to: Community Hospital of Sonoma County, 3325 Chanate Road, Santa Rosa, Ca. 95402 (Dr. Geyman).

\*The author of this article was in private practice in Mount Shasta at the time he submitted it for publication.



TABLE 1.—Treatment Protocols for Coronary Care Nurses

**ARREST PREVENTION PROTOCOL**

(Rhythm strips in all cases)

**First Degree AV Block:**

Watch for increasing block; no treatment

**Second Degree AV Block:**

Atropine 1 mg intravenously (diluted to 10 cc with saline solution).

Isuprel® drip if no response in 5 minutes (1 mg in 500 ml cc D5W; increasing rate to 60/minute, but avoid PVC's).

**Third Degree AV Block:**

Atropine 1 mg intravenously (as above).

Isuprel drip (as above) if no response in 3 minutes.

Levophed® drip if blood pressure below 70 systolic after above steps (2 ampules in 500 ml D5W).

**Premature Ventricular Contractions:**

Unifocal, 5 or more per minute. } Xylocaine®, 25 mg intravenous bolus.

Multifocal (any frequency). } If no response in 2 minutes, give Xylocaine 50 mg intravenous bolus

"R on T" (even if single) } If successful, start Xylocaine drip.

Bursts of ventricular tachycardia. } If unsuccessful, start Pronestyl® drip.

**Ventricular Tachycardia (Sustained):**

Xylocaine 50 mg intravenous bolus.

If no response in 2 minutes, give Xylocaine 100 mg intravenous bolus.

If successful, start Xylocaine drip.

If unsuccessful, start Pronestyl drip, unless physician present prefers to perform countershock.

NOTE: For ventricular tachycardia with blood pressure less than 70 systolic and stupor approaching coma, perform immediate defibrillation.

**Xylocaine Drip:**

50 ml vial of 2 percent Xylocaine in 500 ml D5W.

1 mg Xylocaine/minute 30 microdrops/minute

2 mg Xylocaine/minute 60 microdrops/minute

3 mg Xylocaine/minute 90 microdrops/minute

4 mg Xylocaine/minute 120 microdrops/minute

Maximum of 4 mg per minute in drip.

Watch for hypotension, drowsiness, euphoria, muscle twitching, disorientation, convulsions.

**Pronestyl Drip:**

2 gm Pronestyl in 500 ml D5W (2,000 mg)

Initial rate 30 to 45 drops per minute, slowing as soon as arrhythmia controlled. Watch for hypotension.

Use minimal drip rate needed.

**ARREST PROTOCOL**

Confirm arrest immediately—Note pulse, blood pressure, state of consciousness: Sound alarm. Quickly determine by electrocardiogram whether ventricular fibrillation or asystole.

**If Ventricular Fibrillation:**

Immediate defibrillation (350 watt per second).

If unsuccessful, repeat shock.

If successful, evaluate if need for cardiopulmonary resuscitation, (pulse, blood pressure); start Xylocaine drip and 5 percent sodium bicarbonate drip.

If unsuccessful after two shocks, start cardiopulmonary resuscitation, give epinephrine intravenously (1 ml of 1:1000 epinephrine in 20 ml of saline solution) and start rapid 5 percent sodium bicarbonate drip. Repeat shocks (third and fourth as indicated).

Start Levophed drip as necessary for hypotension (2 ampules, 500 ml D5W), and give epinephrine as above every 4 to 5 minutes if initial defibrillation attempts are unsuccessful.

**If Asystole:**

Sharp blow to chest.

Start cardiopulmonary resuscitation.

Start rapid 5 percent sodium bicarbonate drip.

Add 1 mg Isuprel to 500 ml D5W and start drip.

Levophed drip as above as needed for hypotension.

If unsuccessful, prepare 10 ml of 1:20,000 epinephrine and ml of 10 percent calcium gluconate for intracardiac injection by physician.

**Nursing Training**

It was immediately apparent that the supply of nurses already working in the hospital could not provide sufficient coverage for the coronary care unit. Accordingly, a 62-hour, 4-month course in Coronary Care Nursing was made available to all interested nurses in the general area. Of the 18 nurses who completed this course, 13 were either in part-time nursing or inactive at the time they enrolled. Given locally, with the assistance of internists from adjacent communities, the course followed the format of similar courses at the University of California. The enthusiasm for this type of training that has been reported elsewhere was seen here also. Accreditation of the course with the local junior college made it additionally attrac-

tive. Instead of payment for overtime, a stipend was given to each nurse satisfactorily completing the course.

Training in cardiopulmonary resuscitation was also given to all other hospital personnel, so that the aide on any given shift can also be utilized in an emergency.

Since the opening of the coronary care unit, 2-hour review sessions have been held once each month for teaching and case review. A call schedule allows full coverage of the coronary care unit at all times, mostly by nurses not in full-time nursing.

**Physician Training**

It is important that the director of the coronary care unit take one of the courses being offered in

Intensive Coronary Care at the large medical centers, and that any other interested physicians do likewise when possible. A series of medical staff sessions were held, covering the procedures and protocols of treatment in the coronary care unit. This was sufficient to bring the staff physicians, all of whom were already involved in the treatment of myocardial infarction, to a more sophisticated level of arrhythmia treatment and coronary care unit techniques.

A telemetry system of electrocardiogram interpretation was established between the Mount Shasta Community Hospital and a Berkeley cardiology group. This system was used extensively and all elective and emergency electrocardiograms on patients in the coronary care unit were transmitted. In addition, consultation on rhythm strips by telemetry was occasionally obtained in emergencies.

### Treatment Protocols

In the early deliberations of the Coronary Care Committee it was evident that carefully developed protocols for early treatment by the nurse were extremely important in this small hospital where physicians are often not immediately available. Accordingly, arrest prevention and arrest protocols were developed (Table 1).

### Cost of Coronary Care Unit

A study was made of the hospital's volume, over the previous several years, of patients both with documented myocardial infarctions and those with chest pain requiring hospital admission as possible myocardial infarction. Based on an estimated 75 admissions a year for coronary care, it was decided to install two monitored beds. Each coronary care bed requires at least 100 square feet of space (preferably 120 feet) and additional space for the coronary care nurse's desk and for storage. It became evident that modification of existing ward space would be less expensive than new construction. A five-bed ward, 29 feet by 16 feet (464 square feet) was readily converted to a four-bed facility combining a two-bed recovery room area with a two-bed coronary care unit. Suction and oxygen were piped in to each of the four beds, and sound-proofed movable partitions on ceiling tracks were provided between the beds, affording immediate expansion of any one area by approximately 20 square feet should emergency treatment become

necessary. Combining the recovery room and coronary care unit has made nursing coverage of the coronary care unit more readily attainable by the utilization of the regular recovery room nurse on the day shift during the week.

In addition to a DC defibrillator and pacemaker already in the hospital, the necessary further equipment included one central alarm monitor, two bedside monitor scopes, two wall clocks, one synchronizer, one electrocardiogram machine and two transvenous pacing catheters.

The total expense of the two-bed coronary care unit was approximately \$12,450 (\$6,225 per bed) as follows:

Equipment	\$ 6,500.00
Construction	3,500.00
Nursing Training Stipends	2,100.00
Architect's Fees	350.00
<b>TOTAL</b>	<b>\$12,450.00</b>

### Results

The coronary care unit has been functioning smoothly for 10 months. There have been two deaths. One of those who died was successfully defibrillated 39 times. His initial cardiac arrest occurred on the 18th hospital day when he was on the open ward. The other at the time of death was a patient on the open ward three days after transfer from the coronary care unit.

Sixty-four patients have been treated, 29 with confirmed acute myocardial infarction, an average of six patients per month. At times when the coronary care unit is empty, one of the two beds is used for general acute care if other beds are unavailable in the hospital.

Nursing interest has been maintained at a high level. Community response has been excellent, and a local fund has been established to help with the expenses of the unit.

The mortality rate for patients with acute myocardial infarction in this hospital for the preceding several years ranged from 35 to 40 percent. In the first 10 months of operation of the coronary care unit, the mortality rate for such patients was 7 percent.

It is believed that the presence of the coronary care unit in the hospital has not only improved the efficacy of medical treatment, but has also increased physicians' sensitivity to earlier diagnosis of myocardial infarction in patients with minimal initial symptoms.

## Conclusion

A successful coronary care unit can be organized and operated in a small rural community hospital. The biggest problem involves nursing supply and training, but part-time or previously inactive nurses can be trained effectively. Telemetry electrocardiogram interpretation provides a useful adjunct and method of emergency consultation. Coronary care units in outlying areas can offer modern treatment and decreased mortality to patients with acute myocardial infarction.

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## WOUNDS IN THE VENTRICLE

"A large heart wound in the ventricle is originally tamponaded by the finger. Retention sutures of large size are then placed in as horizontal mattresses. Hemostasis is finally obtained by a 000 running suture. Attempts to close up a large wound in the ventricle by the continuous suture, such as we can do after an open heart procedure while the pump oxygenator has the heart decompressed, will generally fail—the sutures tearing out as you try to put them into the beating heart. Therefore the mattress sutures are placed under the occluding finger and hemostasis is finally obtained with a continuing suture.

"Wounds of the ventricle close to a coronary artery are handled in a somewhat similar manner. They are originally tamponaded with the finger, and then horizontal mattresses are passed underneath the coronary branch and tied so as not to include the coronary. Occasionally, with such an injury a small branch of the coronary artery has been transected. Even though it's not bleeding at the time of surgery, it should be ligated because when the blood pressure returns to normal, it will start bleeding again and necessitate reoperation."

—ARTHUR C. BEALL, JR., M.D., Houston  
Extracted from *Audio-Digest Surgery*, Vol. 16,  
No. 5, in the Audio-Digest Foundation's subscription series of tape-recorded programs.



## Professional Corporations— Recent Developments

HOWARD HASSARD, Esq., Legal Counsel, California Medical Association

*A lengthy, detailed article reviewing legal and tax problems of professional corporations has been withdrawn from this issue of CALIFORNIA MEDICINE. Instead, we are presenting a status report which is simply another chapter in a continuing saga.*

IN THE JUNE issue of this journal\* it was noted that uncertainty as to the tax status of professional corporations was deterring professionals from incorporating, even though the new California statutes permitting incorporation had been in effect for several months. At that time, the Internal Revenue Service was refusing to recognize professional corporations for tax purposes, in spite of repeated defeats in the nation's courts.

In August, the IRS made a public announcement which was widely misinterpreted. This brief announcement stated only that the IRS was conceding that professional corporations should be treated as corporations for tax purposes. A barrage of publicity aimed at professionals by investment houses and others promoting incorporation generally indicated that this statement represented total capitulation by the service. This evaluation did not seem to be supported by the text of the announcement, and those familiar with IRS's traditional hostility toward professional corporations were not so optimistic. It was pointed out that mere recognition of the professional corporation as a taxable entity would not resolve many other tax problems.

Late in October, the Treasury made another announcement. The department, referring to professional corporations as "a loophole," indicated it

would seek corrective legislation next year. On 28 October this threat became a reality when the Senate Finance Committee suddenly amended the tax reform bill, already passed by the House, to deny professional corporations the benefits of qualified corporate pension or profit-sharing plans, except to the extent permitted by the Keogh law.

The fate of this amendment may be determined by the time this issue of CALIFORNIA MEDICINE reaches its readers. Adoption will depend upon action by both the Senate itself and by the joint Senate-House conference committee, which resolves differences in the bill as it left the House and as finally amended in the Senate. While the House version of the 1969 tax revision bill did not include the Senate Finance Committee's measure, a similar, more limited proviso was passed by the House. The House bill would have denied usual corporate retirement plans to "Subchapter S" corporations. Subchapter S corporations, which can have no more than ten shareholders, are those which elect to be treated as partnerships for tax purposes. Many professional corporations would have chosen the Subchapter S election, because it benefits those member-shareholders who cannot afford to reduce their flow of available funds.

The House bill was not aimed at professional corporations. It dealt with all Subchapter S corporations, which would include some professional corporations. The Senate amendment is directed specifically at professional corporations. If adopt-

\*Howard Hassard: Medical Corporations—Some Observations, CALIFORNIA MEDICINE, 110:512-513, 1969.

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ed, the law will limit professional corporations, to the same type of retirement plans as are available to self-employed individuals under the Keogh law. Professional corporations will therefore be limited to a maximum deduction of 10 percent of income or \$2,500, whichever is less, with respect to contributions made on behalf of shareholder employees. In contrast, other corporations are able to make contributions to qualified plans of approximately 25 percent of employee compensation. This advantage has been the principal selling point to many who have considered incorporation of their practice.

If the professional person's retirement plan is subject to the same restrictions, regardless of whether he is self-employed or becomes the employee of his own corporation, the corporation obviously offers no advantage in this regard. The loss of this major advantage is likely to mean that incorporation will not be beneficial to most practitioners, taking all considerations into account. Incorporation still offers some advantages, and some physicians may find incorporation worthwhile, in view of the facts which pertain to their own practice. The large group may choose incorporation for ease of management. Limited liability for the act of associated physicians may also be an advantage. However, as a practical matter, it should be pointed out that the physician is per-

sonally liable for his own malpractice regardless of incorporation, and insurance must be obtained to cover any liability arising from actions of other member physicians, regardless of whether the practice is a partnership or a corporation.

There are also fringe benefits, from a tax standpoint, which only corporations can utilize. These include deductible group term life insurance up to \$50,000 per employee; accident and health insurance; and medical or dental reimbursement plans. On the other hand, there are many tax pitfalls which apply only to corporations. Thorough, competent tax analysis is still essential if incorporation remains a consideration. The corporation must also observe legal formalities in the conduct of its affairs. This necessarily involves additional expense, plus the expenditure of additional time and effort by the physician shareholders responsible for the corporation's affairs.

Physicians, lawyers, and other professional persons will continue to seek legislation to correct the many inequities in their tax treatment. It remains to be seen whether professional corporations will be a part of the eventual solution. At the present time, it appears that the Treasury Department's opposition to these corporations justifies continued caution in this area, regardless of the outcome of the Senate amendment denying the benefits of corporate retirement plans.

### TEACHING THE EMPHYSEMIC PATIENT TO BREATHE

"The emphysema patient can gain great relief from sensations of dyspnea from his physician's reassurance that he can overcome them when he has them. . . . Patients can overcome dyspnea by deliberately holding back their rate of breathing. The reason for this is that when you breathe rapidly, if you're obstructed, the work of breathing increases far out of proportion to the delivery of oxygen or to the improvement of alveolar ventilation. Simply by voluntarily reducing the rate of ventilation . . . to a slow, prolonged rate—easy, complete total expiration—one can feel the sensation of dyspnea fading away. It takes a little almost hypnotic persuasiveness to teach the patient this, but it works."

—BEN V. BRANSCOMB, M.D., Birmingham  
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## EDITORIAL

### Enigma of the Gastroesophageal Junction

FEW PARTS OF THE HUMAN BODY appear so innocuous and yet are so frustrating to anatomists, physiologists and clinicians as the gastroesophageal junction. Removed from its usual location and tacked out on a board, it is an unimpressive bit of tissue consisting of a tube merging into a pouch. The only other notable feature, visible on its inner side, is a rather abrupt change in the lining, which is pale and smooth at the upper, and darker and corrugated at the lower end. This change marks where squamous esophageal mucosa above meets glandular gastric mucosa below. In spite of its deceptively plain looks, the entire gastroesophageal junctional zone may be responsible, wholly or in part, for the major non-malignant disorders that affect man's esophagus: alkali-demanding heartburn, peptic esophagitis (which may hurt, bleed or stenose), lower esophageal (Schatzki) ring, and achalasia.

The very simplicity of the junctional zone defies an unexceptionable explanation of its contributions to the mechanisms of health and disease. There is no universally agreed-on benchmark to serve as a

point of departure for describing the anatomy of the area. Although the word "cardia" is often used to indicate where esophagus opens into stomach, no serosal or mural structure exists to identify the cardia. Neither the shape nor the character of smooth muscle presents a definite line where the wall changes from tube to pouch. Under these circumstances, many rely on the gastroesophageal mucosal junction to separate the two organs. This practice serves convenience but does not necessarily enjoy authenticity. In man, many are convinced, the mucosal junction is not at the approximate location of the cardia, but well above it in a part of the junctional segment that is clearly tubular. In some animals, such as the horse and the rat, on the other hand, the mucosal junction is well down within the gastric pouch, and those who insist that this junction provides the discriminating landmark perforce apply the label esophagus to what is undeniably a sac-like upper half of stomach.

This anatomic no-man's land between stomach and gullet presents the author who would discuss esophageal disease with a major dilemma. Necessarily, if his discussion is to be anchored on basic anatomic and physiologic characteristics, he must draw a bold line and say, "On this side is esophagus; on that, stomach." Drawing a bold line across disputed territory, however, is hazardous. Zboralske and Friedland draw it as shown in Figure 1 of their well-balanced review of esophageal disorders in this issue (page 34). This line (labeled 4 in the figure) is identified as representing the "transverse mucosal fold," which, the authors say, demarcates the gastroesophageal junction and is known by a variety of synonyms, including "lower esophageal ring" or "cardia." Their text does not state definitely that this trans-



verse fold is created by the junction of gastric and esophageal mucosa, but the German words in Figure 3 identify it as such. That any mucosal fold, whatever its nature, exists normally and with any consistency so far on the gastric side of the human gastroesophageal junctional zone is doubtful. If a fold at the location shown in Figures 1 and 3 were as common and clear-cut as the authors suggest, would its illustration require a picture of a foreign anatomy specimen published in 1933?

Is this nit-picking? In its specific aspects, yes, but in its general implications, certainly no. For if an author faces a hazardous dilemma in drawing the exact location of the cardia, so does the clinician who seeks to interpret and treat esophageal symptoms rationally on the basis of abnormal gastroesophageal junctional mechanisms. In the absence of convincingly described and generally accepted anatomic features, the criteria used for diagnosing the presence of a sliding diaphragmatic hernia will be obligingly elastic; the radiologic demonstration of the lower esophageal ring above the level of the diaphragmatic hiatus will not be accepted by all as an unequivocal sign of diaphragmatic hernia; and it is disputable whether a gastroesophageal mucosal junction, found high up in the esophagus of a patient with chronic esophagitis (Barrett's esophagus), is there because of a congenital anomaly or because of upward migration resulting from repeated bouts of esophagitis.

Also shown in Zboralske and Friedland's diagram is an "inferior esophageal sphincter" (number 2) as well as a "vestibule" or "lower esophageal sphincter" (number 3)—which is shown as widely gaping! If all this is confusing, the reason is again anatomic: no clear-cut muscle fibers that might define a sphincter can be identified in the human gastroesophageal junction. Nevertheless, study of the distal esophagus *in situ* (principally by the technique of intraluminal manometry), and of muscle strips *in vitro*, show that the distal few centimeters of the tube portion in the junctional area are more irritable than the remaining esophageal muscle, respond differently, qualitatively and quantitatively, to pharmacologic stimuli, and tend to keep the distal esophageal

lumen closed except when material passes normally from esophagus to stomach, or abnormally in a reverse direction. Non-relaxation of this sphincteric segment is held responsible for the distal esophageal obstruction in achalasia, whereas excessive relaxation, i.e., incompetence, is blamed in whole or in part for excessive gastroesophageal reflux. Hence, if treatment of these disorders is to improve, further studies will have to define, for the internist, the pharmacologic characteristics of the sphincter zone, and, for the surgeon, the influence exerted on sphincteric function by such para-esophageal structures as the phrenoesophageal membrane and the diaphragmatic hiatus. Observations in experimental animals should help to discover the needed knowledge, but in the most commonly used species striated esophageal muscle extends to, or nearly to, the gastroesophageal junction. Man's esophagus, in contrast, is almost unique among mammals in that only its upper third consists of striated muscle; the remainder and the entire gastroesophageal junction are made up of smooth muscle. The only reasonably available experimental animal with human-like esophagus, it is claimed, is the opossum!

Although no dramatic revelation of how the esophagus works has been forthcoming, the general clinical field of esophageal disease has been greatly clarified in the past 25 years by meticulous empirical observation. The varieties of diseases have been classified and hence are more readily recognized. Symptom patterns are now well enough defined to permit reasonably accurate diagnostic impressions, and the radiologic techniques so well illustrated by Zboralske and Friedland usually lead to definitive diagnoses. If doubt remains, endoscopy, biopsy, exfoliative cytology, esophageal sensitivity to acid perfusion (Bernstein test), and measurement of intraluminal pressure and acidity may be called upon. A patient who has difficult or painful swallowing should no longer mystify the doctor—even if that nondescript area where esophagus and stomach join remains an enigma.

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## The Pincers

IT ALREADY SEEMS all too clear that the 1970's will be a decade in which medicine and the health professions will be caught in the jaws of an enormously powerful social, economic and political pincers. Some signs of the inevitable squeeze are even now quite apparent. All the portents are for difficult times ahead. The situation deserves careful examination and considerable planning and preparation.

The jaws of the pincers are easy to identify. One is an evergrowing expectation and demand for better health and more health care. The other is an ever decreasing capability and perhaps even decreasing willingness to pay for it. It is also easy to identify who will be caught, certainly bruised, and possibly crushed in the jaws of the pincers. It will be the medical profession and many other facets of the health care industry. There is certain to be agony, agony born of the frustrations of all concerned. There will be bitterness. There will be enormous wasting of time, effort and money in social, economic and political struggles for control and for survival. Social, economic and political strength, sound planning and practical statesmanship will be at a premium. Medicine and the other health professions must prepare to perform effectively in the patient and public interest in what is certain to be an increasingly tense, trying and often turbulent situation.

The growing expectations of health and health care are deep rooted and not easily to be denied. Health has always been regarded as a good thing. Scientific progress has made better health possible for more people if they receive good health care. This was acknowledged in the health care legislation of the 1960's which sought to convert the possibility into a probability, if not into a reality for all. More recently there has been increasing recognition that health is often a function of human behavior with respect to the physical, social and cultural environment. Many aspects of these relationships will soon become facets of health care and added to the expectations. There is already talk of personal, community, environmental and even species health care.

The other arm of the pincers gains its strength from the harsh reality that there is an end point to the amount of funds from all sources, or the portion of the gross national product, which can or will be made available for health and health care.

There is considerable evidence that this limit is now being approached and may well be reached in this decade. Just as there are no more land, sea or air frontiers, so there is a limit to economic resources. The situation is intensified by an inflationary economy; more sophisticated and therefore costlier health services; earlier obsolescence of training, facilities and equipment as a result of new scientific progress; and the national decision to eliminate charity and low-cost welfare medical care and to pour more money into health care services for more people without first increasing the resources to render these additional services. Thus while the expectations are growing and really infinite, the resources and money to pay the cost are comparatively finite. This finiteness seems destined to become abundantly clear within the next few years.

Health professionals and the whole health care industry may therefore anticipate a decade of tension and squeeze as the arms of the pincers close in upon them. They will be expected to solve unsolvable problems and when they do not they will be blamed and castigated. The process has already begun. The collective guilt and frustration is being projected on to the medical profession which is even now being pilloried and punished for alleged incompetence when good health and good results are not uniformly attained, and for alleged greed and even dishonesty when the costs exceed the available funds. The pharmaceutical industry is already in the same predicament. It may safely be assumed that the orgy has only just begun, and that other health professions and other elements of the health care industry will soon also become victims of undeserved and often vicious social, economic and political attack, if not actual persecution.

If such harassment lasts as long as would seem likely if this analysis of the powerful pincers is correct, there is real danger that permanent damage will be done to the health professions and the health care industry, which could only have serious long-range deleterious effects upon the health and health care of the nation. The only practical defense available at this moment is to develop an improved capability to resist the crushing effect of the pincers. At its November 1969 meeting the Council of the California Medical Association approved the principle of a "crash" program of study and research to develop an improved technology in health care delivery; health care plans and



means of financing them; cost benefit assessment; leadership skills; and action tactics such as the successful use of social, economic and political pressures, the techniques of negotiation and of understanding and influencing public opinion.

It is essential that this timely and significant action of the Council be implemented quickly and imaginatively in order that the medical profession will be strengthened rather than crushed by the squeeze of the pincers, and so be able to perform effectively in the interest of the patient, the public, and more efficient health care in the coming decade.

## Hemoglobin Variants

IN THIS ISSUE of CALIFORNIA MEDICINE, Lie-Injo reports the results of a 39-month survey of hemoglobin and red cell enzyme variation among normal and sick persons in the San Francisco area. Such surveys must, of necessity, rely upon methods which can readily detect chemical or functional differences within each specific class of proteins or upon clinical manifestations produced by protein abnormalities. Many protein variants are "silent" and remain undetected by available techniques. It has been estimated that only about one-quarter of the hemoglobin variants in the population can be identified by routine electrophoresis. The remainder of the theoretically possible amino acid substitutions would not impart a change in the electrical charge of the molecule. Based upon these and other considerations, the probable frequency of hemoglobin variants in a European population has been calculated at 5:1,000.<sup>1</sup>

The present survey confirms the high incidence of Hb S and Hb C in American Negroes. The high gene frequency of these hemoglobins in certain African populations has been attributed to a selective advantage enjoyed by the heterozygotes. Children with sickle trait (Hb SA) appear to have a relatively greater resistance to falciparum malaria than do normal (Hb AA) children, while the homozygotes with sickle cell anemia (Hb SS)

have a definite reproductive disadvantage. Similar selective pressures have been proposed to explain the high frequency of other genetic disorders in particular populations. With these abnormalities, the heterozygotes have few, if any, clinical manifestations. Disease occurs chiefly in the affected homozygotes or in certain combinations of abnormalities (for example, sickle cell-Hb C disease, sickle cell- $\beta$  thalassemia).<sup>2</sup>

Over 100 hemoglobin variants have been identified. The majority have been observed in relatively small numbers of people and only in the heterozygous state. Many of these represent wholly benign "experiments of nature" which impart neither an advantage nor a disadvantage to the affected persons. Other hemoglobin variants produce clinical manifestations in the heterozygous state either because the hemoglobin is unstable or has abnormal functional properties. The survival of the symptomatic heterozygotes is dependent upon the presence of normal hemoglobin within their red cells. Homozygosity for these abnormalities would, in most cases, be lethal.

Persons with unstable hemoglobins exhibit chronic, frequently familial, hemolytic disease.<sup>3</sup> Splenomegaly and dark urine are common but not invariable clinical features. The pigmenturia has been attributed to the presence of dipyrroles which are poorly characterized products of abnormal heme breakdown. Precipitation of the unstable hemoglobin leads ultimately to the destruction of the red cells. The instability of these hemoglobins has varied considerably and the hemolytic disease has ranged from a completely compensated state to life threatening anemia. With Hb Zürich administration of sulfonamides resulted in a marked accentuation of the hemolysis. Some of these hemoglobins cannot be detected by electrophoresis. The diagnosis depends upon the demonstration of an unstable hemoglobin. These hemoglobins form red cell inclusions (Heinz bodies) following the incubation of the cells with oxidative dyes such as brilliant cresyl blue,<sup>4</sup> and also precipitate when buffered hemolysates are incubated at 50 to 55° C for one hour.<sup>5</sup> These studies should be part of the evaluation of any patient with unexplained chronic hemolysis.

Several hemoglobin variants with abnormal oxygen binding characteristics have been described. Hemoglobins with high oxygen affinity are unable to release normal amounts of oxygen to the tissues.<sup>6</sup> The consequent tissue hypoxia stimulates erythro-



poietin production with the development of a compensatory erythrocytosis. The hematocrit values have generally been about 55 percent. These disorders are benign but must be considered in the differential diagnosis of erythrocytosis.

Hemoglobins with low oxygen affinity are incapable of becoming fully saturated with oxygen in the pulmonary circulation.<sup>7</sup> Affected persons may exhibit chronic cyanosis. The displaced oxygen dissociation curve may result in more efficient oxygen delivery, at least under basal conditions. In Hb Seattle, an unstable hemoglobin with low oxygen affinity, low hematocrits (24-33 percent) were shown to represent an adequate compensation for the hemolytic disease.<sup>8</sup>

Five hemoglobin variants have been designated Hb M. In each of these the amino acid substitution results in oxidation of the heme iron in the affected globin polypeptide chains. The ferrihemoglobin (methemoglobin) produces chronic cyanosis which is characteristically of a darker hue than that of deoxyhemoglobin. Although the oxidized half molecule in each of these hemoglobins is incapable of binding oxygen,<sup>9</sup> symptoms attributable to defective oxygen transport have not been a feature of the reported cases.

Perutz and Lehmann<sup>10</sup> have utilized the three dimensional model of hemoglobin constructed from x-ray crystallographic data to examine the probable molecular effect of the reported human hemoglobin variants. Amino acid substitutions on the hydrophilic external surface of the molecule are generally benign even though the recognized substitutions in this category have usually resulted in a change in the electrical charge of the molecule. The substitutions in Hb S and Hb C are in the same position on the exterior of the molecule and interact with other hemoglobin molecules in the red cell to produce polymerization (deoxy Hb S) or crystallization (Hb C). The nature of these molecular interactions is poorly understood.

The unstable hemoglobins result from amino acid abnormalities which alter the forces responsible for the attachment of heme to globin or for maintaining the conformation of the globin chains. These bonding forces are exerted over very small distances between neighboring amino acids in the hydrophobic interior of the molecule. Important chemical bonds may be abolished by the replacement of one hydrophobic amino acid residue by another of different molecular dimensions. Such substitutions may not be detectable by electro-

phoresis although in some cases molecular distortions result in electrophoretic abnormalities. The introduction of a charged residue into the interior of the molecule would permit the entry of water and be, in most cases, a lethal mutation. Unstable hemoglobins have also resulted from defective bonding between subunits which permits dissociation of hemoglobin into monomers.

The normal function of hemoglobin depends upon interactions between the  $\alpha$  and  $\beta$  subunits of hemoglobin which occur during oxygen exchange. The interactions involve changes in the conformation of the tetrameric molecule ( $\alpha_2\beta_2$ ) as well as dissociation of the hemoglobin into dimeric ( $\alpha\beta$ ) subunits. Most of the amino acid abnormalities which primarily compromise hemoglobin function have either directly involved or indirectly influenced the pair of identical subunit contacts where these molecular changes are maximal. The unstable hemoglobins with abnormal heme binding may also exhibit abnormal functional properties.

The hemoglobins M result from the substitution of amino acids which are intimately associated with the iron atom in the heme group. These substitutions remove stabilizing forces which prevent the oxidation of the iron.

Study of the molecular pathology of the human hemoglobin variants has yielded considerable information concerning both the structural basis of protein stability and the relationships between structure and function in hemoglobins. Much of this information will prove valuable in our understanding of inherited defects in other proteins.

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## Universal Health Insurance

UNIVERSAL HEALTH INSURANCE has long been considered by many to be a predictable, even inevitable, consequence of what has gone before. Some view it as the final solution to all the problems of health care, others warn of dire consequences. Whether for good or bad, or more likely both, all the signs indicate that it is an idea whose time is about to arrive. Its advocates are powerful, they are increasingly insistent and they are gathering substantial support. Recently they were joined by the Council of the California Medical Association which voted 23 to 2 "to support the concept of universal health care coverage utilizing multiple methods of financing and free choice of mechanism based on adequate standards of coverage."

Actually this is not the radical departure from long standing policy it might first seem. It is nothing new for the medical profession to support the idea that everyone should be able to get the health care he needs and that the health care he gets should be of high quality. Physicians have donated countless hours of their time in serving this premise over the years. It is also nothing new that health care costs something, and that someone must pay for it. Since it is inconceivable to the medical profession or to the American public to permit anyone to suffer or die untended simply because he could not or would not provide himself with adequate health care coverage, and since changing social attitudes and rising costs have made charity or welfare health care not only unacceptable but actually impractical, it is evident that some kind of universal health care coverage has become essential.

The situation actually has more parallels with the recognized need for universal protection in other areas such as workmen's compensation, automobile financial responsibility, disability and unemployment insurance, all of which are now required by law in California. However, there is no necessity to develop universal health in-

surance as a centralized state or national system of health care as has happened elsewhere in the world. Indeed this must not be permitted to occur. Rather it should somehow preserve and strengthen the peculiarly American tradition of pluralism and free enterprise and apply it in the delivery of health care. There is nothing mutually exclusive about making certain that adequate coverage is truly universal and at the same time providing incentives for healthy competition among a pluralism of plans and mechanisms, permitting consumer recipients to choose and to change among different plans and even to share in the formulation of policy to fit their needs and expectations.

This is the concept of universal health insurance which can and should be supported. It is capable of solving the problems which exist today, and it has the potential to tackle the problems of tomorrow with flexibility and imagination. The specifics should be promptly and expertly developed.

## An Agreement on Style For References

SO MANY ARE the forms for citing bibliographic references in medical journals that readers, turning from one to another, must often be perplexed and nettled until they get the hang of things in each. Uniformity would save their time and patience. To writers who have had a good article turned down by one publication and wish to offer it to another, uniformity of reference style would rid them of the tedious job of changing the form of citation to fit the peculiarities of each journal. To editors and copy-readers uniformity would be a blessing.

To secure that blessing to ourselves and to our readers and writers, CALIFORNIA MEDICINE, walking in the best of company, has joined with a number of well-edited journals in an Agreement to Uniform Style for Bibliographic Citations, and we will convert to that style with the publication of manuscripts that are accepted from now on.

The Agreement grew out of a meeting on the subject, held last May in Atlantic City, in which CALIFORNIA MEDICINE was asked to participate. The form to which we have subscribed, and a list of the journals that have adopted it, follow:

### Cooperating Clinical Journals Atlantic City, 6 May 1969

#### Agreement on Form on Bibliographic Citations

References to journal articles are based on the form used in *Index Medicus*, with these minor departures:

Last name of author followed by initials without internal punctuation, except for commas separating two or more authors: Title of paper with only initial letter of initial word capitalized. Abbreviated journal name using *Index Medicus* form and without abbreviation volume number: first page of article—last page of article with all numerals, year (Note: month and day will not be used in any case.)

#### EXAMPLE:

Podmore DA: Routine determination of urinary pregnadiol using a gas chromatograph with automatic sample application. *J Clin Path* 19:619-621, 1966

#### EXAMPLE OF TWO AUTHORS:

Podmore DA, Smith CK:

Up to three authors will be listed; one or more authors past the third will be designated "et al."

#### EXAMPLE OF MORE THAN THREE AUTHORS:

Poe ND, Dore EK, Swanson LA, et al:

Journal title abbreviations will be those used in *Index Medicus*, listed in the first section of each cumulated volume and available in a reprint (*List of Journals Indexed in Index Medicus*. Available from Superintendent of Documents, U.S. Government Printing Office, Washington, D.C. 20402.)

Journal titles will be cited as they existed at the time of publication (not in a subsequent or present form), but the AMA Archives journals of 1957-60 will not be cited with "AMA."

References to books, theses, and comparable publications will follow this form:

Author's last name initial: Title of book with conventional capitalization. City of publication, publisher, year of publication

#### EXAMPLE:

Berne E: *Principles of Group Treatment*. New York, Oxford University Press, 1966

If a page is cited, the citation follows the year and a comma:

#### EXAMPLE:

Berne E: *Principles of Group Treatment*. New York, Oxford University Press, 1966, p 26

Chapters in books will be treated as journal articles with regard to capitalization:

#### EXAMPLE:

Bond WA: Uric acid lithiasis, chap 2, *Calculi of the Urinary Tract*. Philadelphia, Lea and Saunders, 1962

Other types of citations will be built on these principles.

#### List of Participating Medical Journals

*American Journal of Cardiology*  
*American Journal of Medical Sciences*  
*American Journal of Medicine\**  
*Annals of Internal Medicine*  
*California Medicine*  
*Clinical Research*  
*Gastroenterology*  
*Journal of Chronic Diseases*  
*New England Journal of Medicine*

#### All journals of the American Medical Association:

*American Journal of Diseases of Children*  
*Archives of Dermatology*  
*Archives of Environmental Health*  
*Archives of General Psychiatry*  
*Archives of Internal Medicine*  
*Archives of Neurology*  
*Archives of Ophthalmology*  
*Archives of Otolaryngology*  
*Archives of Pathology*  
*Archives of Surgery*  
*Journal of the American Medical Association*

\*The *American Journal of Medicine* will use only the first page number of a journal article, departing from the agreement to this extent.



# LETTERS *to the Editor*

## Principles and Practice Of Podiatry

*To the Editor:* The book review by William S. Mowrey, M.D., of *Principles and Practice of Podiatry* by Frank Weinstein, D.S.C., (CALIFORNIA MEDICINE 3:341, Oct. 1969) was interesting, constructive and above all, friendly. There were a few comments that I found especially interesting and would comment upon.

Dr. Mowrey expressed surprise that "34 pages of textbook could possibly be devoted to the lifeless horny topic," the reference being to onychology. As I write I have before me the excellent work by V. Pardo-Castello and Osvaldo A. Pardo, *Diseases of the Nails*, published by Thomas, which contains 284 pages. Onychology is a subject of special interest to me and I think my thoughts on the subject that still need stating should encompass another 200 plus pages. Onychology is a most interesting and challenging subject with too much mythology as the basis for treatment.

Dr. Mowrey suggests that though the name of the practice of foot management is now Podiatry that the degree of Doctor of Surgical Chiropody is still the name of the degree. All colleges of podiatric medicine, with a single exception, now issue

the degree of Doctor of Podiatric Medicine, the exception existing because of some legal problems in the state in which it is located. All members of the American Podiatry Association are having their previous degrees changed to D.P.M. as quickly as it is practically possible to do so, state laws being what they are. At the time the Weinstein book was being put together these exchanges had not yet occurred.

I would agree with Dr. Marvin Steinberg (chapter on "Dermatology in Podiatry") that "under no circumstances should x-ray or radium treatment ever be given for warts or any other benign lesion on the human foot," this seems to be what Dr. Mowrey subscribes to as well.

References within the book to areas outside the foot are, in my opinion, proper since it is expected that the podiatrist knows what can be done on structures adjacent to, as well as remote, for the correction of pathologies that affect the function of the foot.

Though the book does not seem to point up the importance of consultation with the various specialties in medicine, as is observed by Dr. Mowrey in his final paragraph, great emphasis is being placed on this in the colleges of podiatry and especially at the California College of Podiatric Medicine. Medical specialists are a part of the clinical faculty where their role as consultants sets the pattern for the practice lives of the podiatrist.

PHILIP GARDNER, D.P.M., F.A.C.F.S.

*Director, Clinical Educational Services  
California College of Podiatric Medicine  
San Francisco*

# Recognition of Pulmonary Embolism

JAMES K. ALEXANDER, M.D.\*

*Material Supplied by the California Heart Association*

THE DIAGNOSIS of acute pulmonary thromboembolism may be derived from history, symptoms, physical findings, electrocardiogram, serum enzymes, chest roentgenogram, pulmonary function tests, isotope lung scan and pulmonary angiography. Of these, angiography is by far the most accurate and specific in detecting the presence and extent of embolic disease. Indeed, angiography may be absolutely necessary to establish the diagnosis in the presence of congestive heart failure, or to differentiate such conditions as atelectasis, pneumonia, acute myocardial infarction and peritonitis.

As the symptoms of acute pulmonary embolism are notoriously protean, the disease may mimic a variety of neurological, cardiovascular, respiratory and upper abdominal disorders. Dyspnea, restlessness and apprehension are common, as are symptoms due to cerebral ischemia such as dizziness, syncope and convulsive phenomena. Dull substernal pain signals massive embolism, and is probably secondary to coronary insufficiency. If pulmonary infarction ensues, pleuritic pain, cough and hemoptysis may develop. Wheezing occurs infrequently with acute pulmonary embolism, although atelectasis and hypoxemia in the affected regions of the lung favor airway narrowing.

Of the findings on examination, hyperpnea is the most consistent, and often the most striking. Though increased physiological dead space is a factor, the mechanism of hyperpnea in man is unknown. Oxygen administration usually produces little effect. Fever, tachycardia and tachypnea are frequent findings. Signs of venous thrombosis in the legs develop in less than half the patients, and may not appear until days or weeks after onset of cardiorespiratory or neurological symptoms. Jaundice is more often due to hepatic dysfunction than

to hemolytic mechanisms, occurring most frequently in association with congestive heart failure or chronic liver disease.

While certain symptoms and signs in an appropriate clinical setting may strongly suggest the diagnosis of pulmonary embolism, these same findings may obtain in other diseases. To establish the presence of acute pulmonary embolism, or to rule it out, additional diagnostic aids are almost always necessary. The conditions presenting differential diagnostic problems most frequently are pneumonia, atelectasis, pericarditis, cholecystitis, dissecting aortic aneurysm, cardiac tamponade, acute myocardial infarction and hyperventilation syndrome.

Appraisal of aids in diagnosis may begin with electrocardiography. In most cases, acute pulmonary embolism results in no definite electrocardiographic abnormality, and the transient nature of the changes, when they do occur, is characteristic. The electrocardiographic findings most commonly observed, namely sinus or supraventricular tachycardia, right axis deviation, right bundle branch block, and inverted T waves in leads  $V_1$  to  $V_3$  or  $V_4$ , may be helpful but are all non-specific.

Elevated serum lactic dehydrogenase (LDH) along with normal serum glutamic oxalacetic transaminase (SGOT) and normal or elevated serum bilirubin favor the diagnosis of pulmonary embolism. However, LDH levels may not rise following embolism, and elevation is a non-specific finding, occurring also with cardiac failure, shock, pregnancy, liver disease, and after surgical procedures. In addition, LDH assay does not differentiate pulmonary infarction from pneumonia.

Chest roentgenographic findings may be suggestive of embolism, but are not often diagnostic. Before frank infarction develops, the chest film may show no abnormality. In some cases, enlargement of main pulmonary arteries or their major branches is discernible, with absent or diminished pulmonary vascular markings peripherally. The hemidiaphragm on the affected side may be elevated, due to atelectatic changes. Pulmonary densities appearing after infarction are typically subpleural, may be transient, are often associated with effusion, and most frequently involve the right lower lobe.

Scintillation scanning of the lungs, after intravenous injection of macro-aggregated human serum albumin particles labeled with  $I^{131}$  or other appropriate radioactive material, is a useful tech-

\*Dr. Alexander is Professor of Medicine, Baylor University College of Medicine, Houston, Texas.

nique in the diagnosis of acute pulmonary embolic disease. Since most of these particles have a larger cross-sectional area than the average pulmonary capillary, they are trapped at precapillary level during the initial transit through the lungs, and the distribution of radioactivity reflects regional pulmonary blood flow. Thus, segments to which the blood supply has been interrupted by occlusive thromboemboli will appear as "cold areas" or areas of diminished radioactivity on the lung scan. This method is advantageous because it is virtually without risk and lends itself well to the performance of serial observations. However, any condition leading to reduced or absent regional capillary perfusion may produce alterations in the lung scan so that reduced radioactivity over the site of a pulmonary infiltrative lesion on the chest film can be anticipated regularly, hence provides no differential diagnostic information. The diagnostic potential of the scanning procedure is greatest when embolism is suspected, but there is little or no abnormality found on the chest film. Even under these conditions, "cold areas" may be found, particularly over lung bullae, in obstructive lung disease, or over the lower lobes with left ventricular failure. Conversely, in some cases little abnormality in the scan may be seen where thromboemboli produce partial but not completely occlusive lesions. Although cautious interpretation is required, the lung scan remains a very useful screening procedure in the

diagnosis of acute pulmonary embolism and, once the diagnosis is established, may provide information regarding the course of the disease and response to therapy.

Visualization of the pulmonary vasculature can be accomplished by either selective or venous angiography. In patients with acute pulmonary thromboembolism, the chief angiographic findings are complete or incomplete obstructions of various pulmonary arterial branches, intra-arterial filling defects, decrease in volume of affected lung segments, and changes in arterial caliber proximal or distal to the obstructive lesions. In other cardiorespiratory diseases such as cardiac failure, pneumonia, pulmonary tumor, abscess, bulla, fibrosis or emphysema, the pulmonary arteries may be compressed, displaced or attenuated, but remain patent to the subsegmental level, showing neither filling defects nor obstructive lesions. Thus it is the identification of specific structural changes within the pulmonary arteries that renders angiography the most definitive diagnostic method available. The decision to perform arteriography ultimately must be a matter of clinical judgment, based on the status of the patient, facilities available, and possible therapeutic implications. Angiographic demonstration of pulmonary thromboembolism would appear essential before pulmonary embolectomy, and highly desirable before interruption of blood flow through the inferior vena cava.

#### MANAGING INFANTS WITH HYPERBILIRUBINEMIA

"Early feeding appears to affect the enterohepatic shunt of bilirubin which, in fetal life, results in the passage into the gut of a fair amount of bilirubin. After the child is born, bilirubin is reabsorbed into the circulation; and early feeding appears to slow the absorption of the bilirubin or promotes its excretion. It makes no difference what is fed in terms of this action on bilirubin—glucose, milk, charcoal, or plain water. It's obvious that early fed infants are less likely to develop high levels of bilirubin than those fed late."

—SYDNEY S. GELLIS, M.D., Boston  
Extracted from *Audio-Digest Pediatrics*, Vol. 15, No. 2, in the Audio Digest Foundation's subscription series of tape-recorded programs.



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# In Memoriam

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## R. STANLEY KNEESHAW, M.D.

DR. R. STANLEY KNEESHAW, a Past President of the California Medical Association (1949-50), died in an automobile accident on the Pacheco Pass Highway near Los Banos, 5 November 1969. It was not immediately determined whether Dr. Kneeshaw died from injuries received in the accident or from a possible heart attack. Dr. Kneeshaw had made a remarkable recovery from a stroke suffered in April 1967.

Dr. Kneeshaw had led a full and vigorous life that was continually marked with intense moments of high valor, personal despair, dedicated community service, and an almost never ending outpouring of human energy. Despite the impact of the temporary physical disability he suffered two years ago, his spirit for recovery remained high, and recover he did. His last day was spent on a duck-hunting trip near the San Luis Dam, and when the day was over, one could almost imagine that friendly voices from out of the past and here now chorused the cliché about the "good man who did get the option to go with his boots on." He was 79 years of age. Dr. Kneeshaw was an avid golfer, collecting many trophies, and he also hunted the West Coast area, Alaska and Minnesota.

Dr. Kneeshaw earned his Bachelor of Science degree from the University of Chicago and his M.D. from Rush Medical School. He served his internship at Washington Boulevard Hospital in Chicago and at Cincinnati General Hospital.

He went overseas in charge of a field hospital in France in World War I, and there he advanced to major. He served in the St. Mihiel and Argonne offensive and was assigned to the Metz sector when the Armistice was signed. Dr. Kneeshaw received several citations and medals from the U.S. Government, as well as foreign countries, for valor and service on the battlefields.

Coming to San Jose in 1920, Dr. Kneeshaw became active in civic affairs and served as county campaign chairman for Governor Goodwin J. Knight's unsuccessful bid for a U.S. Senate seat in 1958.

Posts held by Dr. Kneeshaw include past president, Visiting Nurses' Association; past president, Santa Clara County Medical Society; delegate to American Medical Association eight years; member of International Advisory Committee, College of Surgeons; member of Santa Clara County Water Safety Commission; and member of County Fish and Game Commission.

CLETUS S. SULLIVAN, M.D.

Persons wishing to do so may make contributions to the Physicians' Benevolence Fund to honor the memory of a member who has died. Members of the family will be notified that such a contribution has been made and the name of the donor will be supplied.

Checks should be addressed to Physicians' Benevolence Fund, Inc., California Medical Association, 693 Sutter Street, San Francisco, Ca. 94102.

BAILEY, ARTHUR THOMAS, Palm Springs. Died 25 May 1969 in Palm Springs of bronchopneumonia, aged 76. Graduate of the State University of Iowa College of Medicine, Iowa City, 1916. Licensed in California in 1940. Doctor Bailey was a retired member of the Riverside County Medical Association and the California Medical Association, and an associate member of the American Medical Association.

✧

BORLEY, WILLIAM E., San Francisco. Died 2 November 1969 in Belmont of cancer, aged 64. Graduate of Stanford University School of Medicine, Palo Alto-San Francisco, 1932. Licensed in California in 1932. Doctor Borley was a member of the San Francisco County Medical Society.

✧

CAREY, THOMAS SHERIDAN, Santa Cruz. Died 23 October 1969 at Stanford University Medical Center of cardiovascular arrest, aged 76. Graduate of Stanford University School of Medicine, Palo Alto-San Francisco, 1920. Licensed in California in 1920. Doctor Carey was a retired member of the Los Angeles County Medical Association and the California Medical Association, and an associate member of the American Medical Association.

✧

CONROY, JOSEPH A., Whittier. Died 11 November 1969 in Whittier of acute myocardial infarction, aged 44. Graduate of Duke University School of Medicine, Durham, 1950. Licensed in California in 1955. Doctor Conroy was a member of the Los Angeles County Medical Association.

✧

CORNETT, WILLIAM FREDERICK, Pasadena. Died 30 October 1969 in Pasadena of cardiac arrest, aged 85. Graduate of Queen's University Faculty of Medicine, Kingston, Ontario, 1908. Licensed in California in 1919. Doctor Cornett was a retired member of the Los Angeles County Medical Association and the California Medical Association, and an associate member of the American Medical Association.

✧

DOUGAN, STANLEY, Honolulu. Died 15 November 1969 in Honolulu of cerebral vascular accident, aged 78. Graduate of Stanford University School of Medicine, Palo Alto-San Francisco, 1925. Licensed in California in 1925. Doctor Dougan was a retired member of the Santa Clara

County Medical Society and the California Medical Association, and an associate member of the American Medical Association.



IKUTA, SHUNJI K., Los Angeles. Died 3 July 1969 in Los Angeles of cerebral edema, aged 66. Graduate of the College of Medical Evangelists, Loma Linda-Los Angeles, 1929. Licensed in California in 1929. Doctor Ikuta was a member of the Los Angeles County Medical Association.



KNEESHAW, R. STANLEY, San Jose. Died 5 November 1969 in Los Banos in an automobile crash, aged 79. Graduate of Rush Medical College, Chicago, 1915. Licensed in California in 1920. Doctor Kneeshaw was a retired member of the Santa Clara County Medical Society and the California Medical Association, and an associate member of the American Medical Association.



LAZARD, EDMOND M., Beverly Hills. Died 30 October 1969 in Los Angeles, aged 93. Graduate of the University of Southern California School of Medicine, Los Angeles, 1897. Licensed in California in 1900. Doctor Lazard was a retired member of the Los Angeles County Medical Association and the California Medical Association, and an associate member of the American Medical Association.



LEFFINGWELL, FORREST E., Pasadena. Died 28 October 1969 in Los Angeles of ruptured myocardium, aged 65. Graduate of the College of Medical Evangelists, Loma Linda-Los Angeles, 1933. Licensed in California in 1933. Doctor Leffingwell was a member of the Los Angeles County Medical Association.



MCCLURE, GEORGE, Oakland. Died 16 November 1969 in Oakland of metastatic carcinoma of the liver, aged 77. Graduate of the University of Michigan Medical School, Ann Arbor, 1917. Licensed in California in 1920. Doctor McClure was a retired member of the Alameda-Contra Costa Medical Association and the California Medical Association, and an associate member of the American Medical Association.



MONK, BERT, Los Angeles. Died 12 April 1969 in Alhambra of myocardial infarction, aged 47. Graduate of

the University of California, California College of Medicine, Los Angeles, 1964. Licensed in California in 1965. Doctor Monk was a member of the Los Angeles County Medical Association.



MOORE, JACK K., Temple City. Died 9 November 1969 in Yucca Valley in an airplane crash, aged 63. Graduate of Stanford University School of Medicine, Palo Alto-San Francisco, 1932. Licensed in California in 1932. Doctor Moore was a member of the Los Angeles County Medical Association.



NIELSEN, DAVID I., Newport Beach. Died 17 November 1969 in Newport Beach of cancer, aged 49. Graduate of the University of Nebraska College of Medicine, Omaha, 1945. Licensed in California in 1951. Doctor Nielsen was a member of the Orange County Medical Association.



SAMPSON, JOHN PHILIP, Santa Monica. Died 2 November 1969 in Santa Monica of hemorrhage of colon due to diverticulosis, aged 67. Graduate of Stanford University School of Medicine, Palo Alto-San Francisco, 1930. Licensed in California in 1930. Doctor Sampson was a member of the Los Angeles County Medical Association.



SCHMIDT, ELMER JACOB, Fresno. Died 28 October 1969 in Fresno, aged 78. Graduate of the University of Illinois College of Medicine, Chicago, 1919. Licensed in California in 1921. Doctor Schmidt was a retired member of the Fresno County Medical Society and the California Medical Association, and an associate member of the American Medical Association.



SEIGER, HARRY WRIGHT, Santa Monica. Died 2 November 1969 in Santa Monica of arteriosclerotic vascular disease, aged 69. Graduate of the University of Kansas School of Medicine, Lawrence-Kansas City, 1925. Licensed in California in 1928. Doctor Seiger was a member of the Los Angeles County Medical Association.



WITLIN, ABRAHAM ALLAN, Downey. Died 5 November 1969 in Downey, aged 47. Graduate of College of Osteopathic Physicians and Surgeons, Los Angeles, 1945. Licensed in California in 1945. M.D. degree from California College of Medicine, 1962. Doctor Witlin was a member of the Los Angeles County Medical Association.

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# **1970 ANNUAL SCIENTIFIC ASSEMBLY**

**of the California Medical Association**

**San Francisco, March 7-11**

**Detailed program follows on page 102**

*Topics of the three general meetings:*

**What is family practice?**

**Manpower — new aids to the physician**

**Systems of delivery for health care services**

*Renowned Speakers Are:*

**LYNN P. CARMICHAEL, M.D.**  
Director, Division of Family Medicine  
University of Miami School of Medicine

**JEROME POLLACK**  
Associate Dean for Medical Care Planning  
Harvard Medical School

**MIKE GORMAN**  
Executive Director  
National Committee Against Mental Illness  
Washington, D. C.

**HENRY K. SILVER, M.D.**  
Professor of Pediatrics  
University of Colorado Medical Center

**EUGENE A. STEAD, JR., M.D.**  
Department of Medicine  
Duke University Medical Center

## **L. HENRY GARLAND MEMORIAL LECTURE — MARCH 8**

**Guest Speaker:** Melvin P. Judkins, M.D., Professor of Radiology and Director, Cardiovascular Laboratories, University of Oregon Medical School.

**Title:** "A Breakthrough in the Battle with Coronary Artery Obstructive Disease."



application for **HOTEL ACCOMMODATIONS**  
**NINETY-NINTH Annual Session**

**CALIFORNIA MEDICAL ASSOCIATION • MARCH 7-11, 1970**

**SAN FRANCISCO HILTON HOTEL, SAN FRANCISCO**

**HOUSE OF DELEGATES OPENING SESSION, HILTON HOTEL, SATURDAY EVENING, MARCH 7;  
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2. Your reservation request should include the definite date and hour of your arrival and departure.
3. All reservations must be made through the CMA Housing Bureau, Suite 260, Fox Plaza, San Francisco, California 94102, by February 6, 1970.
4. **CANCELLATIONS:** Please notify CMA Housing Bureau, Suite 260, Fox Plaza, San Francisco 94102 of all cancellations up to 15 days before Annual Session. Within last 15 days, make cancellations directly with hotel.
- CHANGES:** All other changes to be made directly with hotel at all times. Rooms will not be held after 6 P.M. unless a later arrival time has been requested. Failure to notify the hotel of any change in your arrival time may result in cancellation of your reservation.

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<b>CLIFT HOTEL</b> .....	none	25-35	none
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<b>HANDLERY INN</b> .....	none	27-30	none
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**THE NAME AND ADDRESS OF EACH HOTEL GUEST MUST BE LISTED.** Include names and addresses of *each* person in a double or twin-bedded room, and names and addresses of *all other persons* for whom you are requesting reservations.

Your Name:..... Officer?..... Delegate?..... Alternate?..... Speaker?.....

Address:..... County.....

City and State..... Zip Code.....

**GUESTS' NAMES AND ADDRESSES:**

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# PUBLIC HEALTH REPORT

Louis F. Saylor, M.D., M.P.H., Director, State Department of Public Health

## California's Cancer Quackery Law

FOR MORE THAN A DECADE, legislation to control cancer quackery has protected Californians. Beginning in 1957 the California Medical Association, responding to pioneering efforts of Doctors John W. Cline, L. Henry Garland, David A. Wood and others, supported legislative proposals against quackery and in 1959 such legislation was first enacted as law for a trial period of 6 years.

The law named the State Department of Public Health as enforcement agency to control medical quackery in diagnosis and treatment of cancer and authorized the establishment of a Cancer Advisory Council. The 15-member Council is composed of physician and surgeon representatives of six schools of medicine in California, three other practicing physicians and surgeons, two representatives of nonprofit cancer research institutes, three persons who are not physicians and surgeons, and the Director of Public Health, who serves as an ex-officio member. A small staff within the Department acts in executive capacity for the Council and gathers evidence, as authorized by law.

In 1965 the law was renewed, this time with a 2-year expiration date. A resolution was also adopted which provided for an interim study of the problem of cancer quackery by the Assembly Committee on Public Health and Safety. In September 1966 a hearing took place before this committee. Ten persons testified and demonstrated against the law, three of them representing groups calling themselves the National Health Federation and the International Association of Cancer Victims and Friends, the other seven as individuals. Despite this opposition, the Committee recommended enactment of a new cancer quackery law with substantial changes in wording and provisions.

In 1967 this cancer law introduced by Assemblyman Gordon W. Duffy of Hanford passed the Legislature, once more with a 2-year time limit.

The Assembly Committee retained the following valuable features of the earlier law: an Advisory Council of experts, flexible enforcement methods by cease-and-desist orders, injunctions or criminal prosecutions, and authorization for the Department to make contractual arrangements with public and private agencies, such as clinics, hospitals or the National Cancer Institute.

In addition, the law clarified the Department's authority to adopt prohibitory regulations. It made approval of an application under the Federal Food, Drug and Cosmetic Act, or a similar application approved by the California State Board of Public Health, a requirement for selling, prescribing or administering a drug or device to be used in diagnosing or treating cancer. The Board of Health later adopted by reference as parts of the California Administrative Code several sections of federal regulations which outline procedures whereby qualified experts might conduct clinical trials on new drugs or devices, if they have been shown to be safe and to have promise.

The law made a violation of any of the provisions of the chapter, the regulations or any valid order issued by the Department a misdemeanor, and violation of a cease-and-desist order unprofessional conduct. It permitted the issuance of an injunction if a cease-and-desist order were violated. The law placed the burden of proof of efficacy and safety of a cancer agent on the proponent.

In 1969 Senator Lewis F. Sherman of Oakland introduced SB660, a new cancer quackery bill with the same provisions as the 1967 law. This time it was enacted as permanent legislation in Chapter 7, Health and Safety Code. The State Health Department's Cancer Diagnosis and Therapy Evaluation Unit is now consolidated with the Fraud Section of the Bureau of Food and Drug in the Environmental Health and Consumer Protection Program.

Since enactment of the first cancer quackery law the Department has made 104 investigations resulting in 36 convictions with 6 cases pending as of 1 October 1969. Two cases in which criminal convictions were obtained were appealed to the U.S. Supreme Court which upheld the findings of the lower courts.

Convicted individuals included ten doctors of medicine, seven doctors of medicine who were former osteopathic physicians, one osteopathic physician, eleven chiropractors, and seven lay persons. In a number of investigations conducted on individuals who were suspected of questionable practices because of previous complaints, it was not possible to confirm the complaints. However, 22 of these practitioners admitted that because of the cancer law, they denied treatment to cancer patients fearing loss of license or jail terms. This demonstrates that the law has a deterrent effect.

During 1968-69 an effort was made to get data on the magnitude of the cancer quackery problem among Californians. Previously, the only figures available were from the Federal government which estimated the cost of medical quackery in the nation at from 1 to 2 billion dollars. Based on this estimate and on population, California's contribu-

tions to medical quackery would be estimated at between 100 and 200 million dollars.

Questionnaires were sent to a random sampling of 773 physicians signing death certificates on cancer patients asking for information about unorthodox care given to cancer patients by other physicians. Responses were received from 760 physicians, a remarkable record in itself. One hundred and five, or 1 in 7, knew of instances in which 175 patients had received unorthodox treatment. In nine instances the doctors' own patients were involved.

The extent of unorthodox cancer treatment is also suggested by a study of a cancer clinic in Tijuana, Mexico, known to be dispensing remedies banned in California. When it was placed under surveillance for several weeks an average of 55 persons per day were seen arriving and entering the clinic, almost all arriving in cars with California licenses.

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# CONTINUING EDUCATION ACTIVITIES IN CALIFORNIA AND HAWAII

## COMMITTEE ON CONTINUING MEDICAL EDUCATION

THIS BULLETIN of information regarding continuing education programs and meetings of various medical organizations in California and Hawaii is supplied by the Committee on Continuing Medical Education of the California Medical Association. In order that they may be listed here, please send communications relating to your future meetings or postgraduate courses to Committee on Continuing Medical Education, California Medical Association, 693 Sutter Street, San Francisco 94102; or phone: (415) 776-9400, extension 241.

### KEY TO ABBREVIATIONS AND SYMBOLS

Medical Centers and CMA Contacts  
for Information

- CMA:** California Medical Association  
Contact: Continuing Medical Education, California Medical Association, 693 Sutter Street, San Francisco 94102. (415) 776-9400, ext. 241.
- LLU:** Loma Linda University  
Contact: John E. Peterson, M.D., Associate Dean for Research Affairs, Loma Linda University School of Medicine, Loma Linda 92354. (714) 796-7311.
- PMC:** Pacific Medical Center  
Contact: Arthur Selzer, M.D., Chairman, Education Committee, Pacific Medical Center, Clay and Webster Streets, San Francisco 94115. (415) 931-8000.
- STAN:** Stanford University  
Contact: Thomas A. Gonda, M.D., Associate Dean, Stanford University School of Medicine, 300 Pasteur Drive, Stanford 94305. (415) 321-1200, ext. 5940.
- UCD:** University of California, Davis  
Contact: Charles J. Thupper, M.D., Dean, University of California, Davis, School of Medicine, Davis 95616. (916) 752-0381.
- UCI:** University of California—California College of Medicine, Irvine  
Contact: Robert Combs, M.D., Associate Dean, University of California, Irvine—California College of Medicine, Irvine 92664. (714) 833-5991.
- UCLA:** University of California, Los Angeles  
Contact: Donald Brayton, M.D., Associate Dean and Head, Continuing Education in Medicine and the Health Sciences, 15-39 Rehabilitation Center, UCLA Center for the Health Sciences, Los Angeles 90024. (213) 825-6514.
- UCSD:** University of California, San Diego  
Contact: Clifford Grobstein, Ph.D., Dean, University of California, San Diego, School of Medicine, La Jolla 92038. (714) 453-2000.
- UCSF:** University of California, San Francisco  
Contact: Seymour M. Farber, M.D., Dean, Educational Services and Director, Continuing Education, Health Sciences, University of California Medical Center, San Francisco 94122. (415) 666-1692.
- USC:** University of Southern California  
Contact: Phil R. Mannings, M.D., Associate Dean, Postgraduate Division, University of Southern California School of Medicine, 2025 Zonal Avenue, Los Angeles 90088. (213) 225-1511, ext. 203.

## CANCER

- January 24—**Problems in Head and Neck Cancer.** PMC. Saturday. Team approach by various specialists to decisions required in management of malignancies in the head and neck region. Radiation necrosis of the mandible; anesthesia—endotracheal intubation, hypotensive anesthesia; pitfalls; surgery of the head and neck tumors. \$40. 5 hrs.
- February 21-25—**Current Concepts in Cancer Chemotherapy.** UCLA at El Mirador Hotel, Palm Springs. Saturday-Wednesday. 13½ hrs.
- May 15-16—**Hormones and Neoplasia—Cancer Conference.** USC at Century Plaza Hotel, Los Angeles. Friday-Saturday.

## MEDICINE

- January 16-17—**Modern Trends in Epilepsy.** UCSF. Friday-Saturday. Critical analysis of team approach, epilepsy in childhood, re-appraisal of petit-mal, metabolic aspects of epilepsy and anticonvulsants, EEG and epilepsy, treatment of refractory epilepsy, neurosurgery of epilepsy, epilepsy and personality, focal epilepsy, epilepsy and the law, medical and social problems of epilepsy. \$30. 12 hrs.
- January 16-18—**Total Rehabilitation—A Road to Work for "Unemployable" Cardiac Patients.** Ben R. Meyer Rehabilitation Center of Cedars-Sinai Medical Center at Sheraton-Universal Hotel, Los Angeles. Thursday-Sunday. Contact: John H. Aldes, M.D., Director, Ben R. Meyer Rehabilitation Center, 4833 Fountain Ave., Los Angeles 90029. (213) 662-9111.
- January 17—**Workshop in Advanced Arrhythmias.** PMC. Saturday. Review of electrophysiological bases, mechanism, diagnostic approach and significance of complex disturbances of cardiac rhythm. \$50. 7 hrs.
- January 20-31—**Coronary Care Unit Program for Physicians.** CRMP Area V at Los Angeles County-USC Medical Center. Two week course repeated monthly through May, 1970. Arrhythmia detection, diagnosis and therapy, defibrillation and cardioversion, central venous pressure monitors, placement of pacing catheters, new aspects in diagnosis and treatment of congestive heart failure, shock and associated respiratory problems, and CCU management in community hospitals. Contact: Gladys Ancrum, Dr. P. H., Administrative Associate, CRMP Area V, 1 West Bay State St., Alhambra 91801. (213) 576-1626.
- January 21—**14th Annual Midwinter Symposium on Cardiovascular Research.** Los Angeles County Heart Association at Hilton Hotel, Los Angeles. Wednesday. Contact: Joe Kennelley, Director, Public Information, LACHA, 2405 West 8th St., Los Angeles 90057. (213) 385-4231.
- February 2-3—**Symposium of Arrhythmias.** American College of Cardiology in cooperation with UCI at Newporter Inn, Newport Beach. Sunday-Tuesday. Latest anatomical, pharmacological, and physiological bases for disturbances of cardiac rhythm related to specific disease entities and situations. Workshops will demonstrate clinical application of basic concepts. \$60 members, \$75 non-members. 11 hrs. Contact: UCI.
- February 3-14—**Coronary Care Unit Program for Physicians.** CRMP Area V. See January 20-31.

February 4-March 4—**Toxicology in Modern Medicine.** UCLA. Wednesdays 7:30-9:30. 10 hrs.

February 6—**Stroke Symposium.** CRMP Area VII at Hotel Del Coronado, Coronado. Friday. \$10. Contact: Derek W. Price, Assoc. Coordinator, CRMP Area VII, 7816 Ivanhoe, La Jolla 92037. (714) 459-3739.

February 12-13—**Effects of Steroids in Erythropoiesis and Bone Marrow Failure.** UCSF. Thursday-Friday.

February 13-14—**American College of Physicians — Northern California-Nevada Regional Meeting.** Mark Thomas Inn, Monterey. Friday-Saturday. \$5. Contact: John R. Gamble, M.D., Governor, No. Calif. and Nevada Region, ACP, 655 Sutter Street, San Francisco 94102. (415) 673-4080.

February 14-15—**Rheumatic Diseases in Children and Adults.** USC at Childrens Hospital, Los Angeles. Saturday-Sunday.

February 17-18—**American College of Physicians — Hawaii Regional Meeting.** Pacific Club, Honolulu. Tuesday-Wednesday. Tuesday and Wednesday a.m.: Scientific Sessions. Tuesday p.m.: Lecture in connection with The American College of Surgeons, "What's Left in Thyroid Disease for the Surgeon?" 8 hrs. Contact: Morton E. Berk, M.D., Governor, Hawaii Region, ACP, 1133 Punchbowl Street, Honolulu 96813. (808) 537-2211.

February 18—**Coronary Heart Disease, 1970.** USC at Huntington-Sheraton Hotel, Pasadena. Wednesday 9-4:30. Latest research and clinical information on diagnosis and management of coronary disease. Prevention and post-coronary rehabilitation. \$35. 6 hrs.

February 20-21—**American College of Physicians — Southern California Regional Meeting.** Coronado. Friday-Saturday. Contact: Eugene Braunwald, M.D., Chairman of Scientific Program, UCSD.

February 28-March 1—**Your Patient with Renal Disease.** UCSF at Franklin Hospital, San Francisco. Saturday-Sunday. Office recognition and evaluation, recurrent urinary tract infections, hypertension, current vascular surgical concepts in reno-vascular hypertension, urological aspects, acute and chronic renal failure, chronic hemodialysis, the community dialysis unit. 8½ hrs.

March 2-20—**Coronary Care for Physicians Training Program.** CRMP Area IV and Cedars-Sinai Medical Center at Cedars of Lebanon Hospital, Los Angeles. Three week course repeated six times through November, designed for practicing internists or cardiologists who will subsequently be working in or directing CCU in community hospitals. Electrocardiography, physical diagnosis, CCU planning and administration, electrolytes and acid-base metabolism, emphasis on practical techniques. Contact: Herbert Stein, M.D., Coronary Care for Physicians Training Programs, Dept. of Cardiology, Cedars of Lebanon Hospital, Box 54265, Los Angeles 90029. (213) 662-9111, Ext. 306.

March 3-14—**Coronary Care Unit Program for Physicians.** CRMP Area V. See January 20-31.

March 5-6—**Symposium on Endocrinology.** USC at Century Plaza Hotel. Thursday-Friday. Modern endocrine testing, reproductive endocrinology, general endocrinology.

March 5-6—**Dialogues in Dermatology.** UCSF at Sir Francis Drake Hotel, San Francisco. Thursday-Friday. Veterinary dermatology; atopic dermatitis. The Perineum: vulvar dermatology; genito-urinary dermatology; proctologic dermatology; stomatology and the dermatologist; oto-dermatology; blepharitis; current advances in burn therapy; podiatric dermatology; stasis dermatitis and ankle ulcers; research dermatology. 14 hrs.

March 7 — **Pediatric Hematology.** UCSF at Childrens Hospital and Adult Medical Center, San Francisco. Saturday.

March 14—**Auscultation of the Heart.** PMC. Saturday. Discussion and teaching on the heart sound simulator. 8 hrs.

March 26—**Obesity.** USC at Hilton Hotel, Los Angeles. Thursday.

April 3-4—**Cardiac Arrhythmias in Clinical Practice.** Sacramento-Yolo-Sierra Heart Association at Sacramento Inn, Sacramento. Friday-Saturday. \$10. 10 hrs. Contact: Harold M. Lowe, M.D., Chairman, Symposium Committee, Sacramento-Yolo-Sierra Heart Assoc., Dept. of Cardiovascular-Pulmonary Diseases, Mercy Hospital, 4001 J Street, Sacramento 95819. (916) 456-7881.

April 6-15—**Cardiology for the Consultant—A Clinician's Retreat.** American College of Cardiology at Rancho Santa Fe Inn, Rancho Santa Fe. Ten day program for well-trained clinicians to sharpen ability in the field of cardiology. Contact: William D. Nelligan, Exec. Dir., ACC, 9650 Rockville Pike, Bethesda, Md. 20014. (301) 530-1600.

April 8-9—**Medical Surgical Gastroenterology.** USC at Hilton Hotel, Los Angeles. Wednesday-Thursday.

April 10—**Annual Symposium on Heart Disease.** Orange County Heart Association at Disneyland Hotel, Anaheim. Friday. Contact: Liggett McLaws, Program Dir., OCHA, P.O. Box 1704, Santa Ana 92702. (714) 947-3001.

April 11—**Myocardial Infarction.** PMC. Saturday. Principles and techniques in a coronary care unit, electrocardiographic diagnosis, therapeutic approach to arrhythmias, heart failure in myocardial infarction, cardiac rehabilitation and the value of exercise, anticoagulation. \$35.

April 11-12—**Clinical EMG.** UCSF. Saturday-Sunday.

April 22-25—**Advances in Endocrinology and Metabolism.** UCSF. Wednesday-Saturday. Intensive review of interrelationships between metabolic disease and endocrine dysfunction, critical evaluation of new developments.

May 4-22—**Coronary Care for Physicians Training Program—CRMP Area IV.** See March 2-20.

May 12—**Analytical Approach to Cardiac Diagnosis.** American College of Cardiology and LLU at LLU. Tuesday. Representative cases of heart disease: history, examination, laboratory and radiological procedures. Contact: William D. Nelligan, Exec. Dir., ACC, 9650 Rockville Pike, Bethesda, Md. 20014. (301) 530-1600.

May 14-15—**Diagnosis and Clinical Management of Ocular Infections.** UCLA. Thursday-Friday.



May 15-17—**Basic Principles of Cardiac Therapy.** PMC and the American College of Cardiology at Jack Tar Hotel, San Francisco. Friday-Sunday. Clarification of pathophysiological basis of various disease states, rational approach to drug usage. 24 hrs. Contact: PMC.

Continuously—**Basic Home Course in Electrocardiography.** One year postgraduate series, ECG interpretation by mail. Physicians may register at any time. \$100 (52 issues). Contact: USC.

## Grand Rounds—Medicine

### Tuesdays

9-10:30 a.m., Assembly Hall, Harbor General Hospital, Torrance. UCLA.

### Wednesdays

Grand Rounds in Internal Medicine. 10:30-12:00 noon. Auditorium, Medical Sciences Building. UCSF.  
11:00 a.m., Room 1645, Los Angeles County-USC Medical Center. USC.

12:30 p.m., Auditorium, School of Nursing, Orange County Medical Center. UCI.

Grand Rounds in Internal Medicine. 12:30-1:30 p.m., University Hospital, UCSD.

### Thursdays

10:30-12:00 noon, Room C3-105, UCLA Medical Center. UCLA.

### Fridays

8:00 a.m., Courtroom, Third Floor, Kern County General Hospital, Bakersfield. CRMP Area IV.

8:30 a.m., Auditorium, Lebanon Hall, Cedars of Lebanon Hospital, Los Angeles. CRMP Area IV.

Infectious Disease Grand Rounds. 10:00 a.m., Auditorium, Childrens Division Building, Los Angeles County-USC Medical Center, Los Angeles. USC.

Neurology. 10:15 a.m., Neurology Conference Building 7, V.A. Hospital, Palo Alto. STAN.

1st and 3rd Fridays, 11:00 a.m., Auditorium, Brown Building, Mount Sinai Hospital, Los Angeles. CRMP Area IV.

1:15 p.m., Lieb Amphitheater, Timken-Sturgis Research Bldg., La Jolla. Scripps Clinic and Research Foundation.

2-3:00 p.m., Classroom, Third Floor, Fresno General Hospital. Fresno. CRMP Area IV.

Rheumatology Grand Rounds. 11:45 a.m., Room 6441, Los Angeles County-USC Medical Center, Los Angeles. USC.

## OBSTETRICS AND GYNECOLOGY

February 7-8—**Los Angeles Obstetrical and Gynecological Forum—19th Annual Meeting.** Beverly Hilton Hotel, Beverly Hills. Saturday-Sunday. Saturday: the fetus in jeopardy, infections in obstetrics and gynecology. Sunday: 1970 Ob. and Gyn. Assembly. Contact: Dee Davis, Executive Sec., L.A. Ob. & Gyn. Soc., 5410 Wilshire Blvd., Los Angeles 90036. (213) 931-1621.

February 20-21—**Birth Prevention: The Growing Challenge to Physicians and to the Community.** UCSF. Friday-Saturday. Birth prevention, contraception, role

of contraceptive clinic, unmarried teenager, sex education in schools, use and complications of IUD and Pill, patient attitudes, future methods, therapeutic abortion, physician attitudes toward therapeutic and elective abortion, techniques of therapeutic abortion, female sterilization. 11½ hrs.

May 15-16—**Obstetrics and Gynecology Symposium.** Southern California Permanente Medical Group and Kaiser Foundation Hospitals at Beverly Hilton Hotel, Beverly Hills. Friday-Saturday. Contact: Shirley Gach, Rm. 6014, So. Calif. Permanente Med. Group, 4900 Sunset Blvd., Los Angeles 90027. (213) 663-8411.

## PEDIATRICS

January 17—**Current Concepts in the Management of Renal Disease in Children.** Childrens Hospital of Orange County. Saturday. 4 hrs. Contact: Merl J. Carson, M.D., Medical Dir., Childrens Hospital of Orange County, 1109 W. La Brea, Orange 92668. (714) 538-8831.

February 7—**Pediatric Urology—The Dilated Ureter; The Uncoordinated Bladder.** UCSF at Childrens Hospital, San Francisco. Saturday. Mechanics of dilatation, diagnostic techniques, hydroureter and reparative ureteral surgery, treatment. \$25. 6½ hrs.

February 9-20—**Mental Retardation.** UCLA in cooperation with Pacific State Hospital, Pomona, at UCLA Neuropsychiatric Institute. Two weeks. For physicians and allied professionals. Causation, symptomatology, care, treatment and management, diagnostic techniques suitable for office practice, parental reactions and intra-family psychopathology, and recent research findings. 80 hrs. Contact: UCLA.

March 7—**Pediatric Hematology.** UCSF. See Medicine, March 7.

March 12-14—**Pediatric Neurology.** UCSF. Thursday-Saturday. Review of neurological examinations and procedures, paroxysmal neurological disorders, metabolic problems in pediatric neurology, disorders of movement.

March 20-21—**Pulmonary Disease in Newborns.** UCI, CRMP Area VIII in cooperation with the National Cystic Fibrosis Research Foundation at Childrens Hospital of Orange County. Friday-Saturday. Registration by March 1 is necessary. Contact: Bruce D. Ackerman, M.D., Dept. of Pediatrics, UCI.

March 30-April 2—**Clinical Evaluation of Children with Learning Disorders.** UCSF. Monday-Thursday. Discussions and demonstrations of the total clinical evaluation: pediatric, ophthalmologic, speech, audiology and educational factors.

April 3-4—**Pediatric Symposium—Nephrology.** Southern California Permanente Medical Group and Kaiser Foundation Hospitals at Ambassador Hotel, Los Angeles. Friday-Saturday. Contact: Shirley Gach, Rm. 6014, So. Calif. Permanente Med. Group, 4900 Sunset Blvd., Los Angeles 90027. (213) 663-8411.

April 4-5—**Armchair Allergy.** PMC. Saturday-Sunday. Early diagnosis, role of steroids in management of asthma, skin tests, current concept of the basic steps in the allergic reaction. \$50.

April 17-18—**Infectious Diseases.** UCSF at Childrens Hospital, San Francisco. Friday-Saturday. For pedia-



tricians, family physicians, internists and clinically oriented bacteriologists.

May 7-9—**Advances in Pediatrics.** UCSF. Thursday-Saturday. Review of major reappraisals in some aspects of the specialty, clinical implications of advances in cytology, physiology, immunology and endocrinology.

### Grand Rounds—Pediatrics

#### Tuesdays

8:30 a.m., Auditorium, Childrens Division Building, Los Angeles County-USC Medical Center, Los Angeles. USC.

8:30 a.m., Conference Room, Sixth Floor, Harbor General Hospital, Torrance. CRMP Area IV.

8:30 a.m., Room 4-A, Kern County General Hospital, Bakersfield. CRMP Area IV.

8:30 a.m., Pathology Auditorium, San Francisco General Hospital.

#### Wednesdays

8:9:00 a.m., held alternately at Auditorium, Orange County Medical Center and Auditorium, Childrens Hospital of Orange County. UCI.

8:30 a.m., Bothin Auditorium, Childrens Hospital, San Francisco.

#### Thursdays

8:30-10:00 a.m., Room 664, Science Building, UCSF.

8:30-9:30 a.m., Lebanon Hall, Cedars of Lebanon Hospital, Los Angeles.

#### Fridays

8:00 a.m., Lecture Room, A Floor, Health Sciences Center, UCLA. CRMP Area IV.

8:30 a.m., Stanford University Medical Center, Palo Alto.

8:9:00 a.m., Lecture Hall, Childrens Hospital of Los Angeles.

### PSYCHIATRY

January 17-18—**Social and Emotional Problems of Poverty.** USC Division of Postgraduate Psychiatry at Ambassador Hotel, Los Angeles. Saturday-Sunday. \$25. Contact: Ronald A. Markman, M.D., Asst. Dir., Postgraduate Psychiatry, USC. (213) 225-1511, ext. 336.

January 20-April 7—**Psychiatric Principles in a Medical Practice.** USC Division of Postgraduate Psychiatry at South Coast Community Hospital Auditorium, South Laguna. Tuesdays. \$35. Contact: Ronald A. Markman, M.D., Assistant Dir., Postgraduate Psychiatry, USC. (213) 225-1511, ext. 336.

February 26-April 30—**Teaching Clinics in Psychiatry.** UCLA. Thursdays.

March 14-15—**Current Theories in Psychiatry.** UCSF at Napa State Hospital, Imola. Saturday-Sunday.

March 14-15—**The Troubled Adolescent in the Modern Family.** UCSF at Mendocino State Hospital, Talmage. Saturday-Sunday.

March 20-21 — **Suicide Prevention and Advanced Workshop.** UCSF. Friday-Saturday.

March 23-26—**American Orthopsychiatric Association.** Mark Hopkins and Fairmont Hotels, San Francisco. Monday-Thursday. Contact: Marion F. Langer, Ph.D., AOA, 1790 Broadway, New York 10019. (212) 586-5690.

April 4-5—**The Brain and Behavior.** UCSF at Agnews State Hospital, San Jose. Saturday-Sunday. New developments in chemistry, neuroanatomy, and neurophysiology related to human behavior.

April 8-June 10—**Group Methods.** UCSF at V.A. Hospital, San Francisco. Wednesdays 11:30-1:00. Weekly lectures and participants assigned to clinic groups. \$25.

April 18-19—**New Approaches to the Care of the Suicidal Patient.** UCLA. Saturday-Sunday.

May 2-3—**Further Explorations in Group Therapy.** UCSF at Modesto State Hospital Modesto. Saturday-Sunday.

May 10—**American Academy of Psychoanalysis—Annual Meeting.** Jack Tar Hotel, San Francisco. Friday-Sunday. Contact: Mollie Carroll, 125 East 65th Street, New York 10021. (212) 879-8950.

May 8-10—**Society for Biological Psychiatry.** Hilton Hotel, San Francisco. Friday-Sunday. Contact: George N. Thompson, M.D., Sec.-Treas., SBP, 2010 Wilshire Blvd., Los Angeles 90017. (213) 483-7863.

May 8-11 — **American Psychoanalytic Association.** Sheraton Palace Hotel, San Francisco. Friday-Monday. Contact: Mrs. Helen Fischer, Exec. Sec., APA, 1 East 57th Street, New York 10022. (212) 265-0430.

May 9-10—**Psychiatry and the Law.** UCSF at Humboldt State College, Arcata. Saturday- Sunday.

May 10—**Association for the Advancement of Psychotherapy.** Civic Auditorium, San Francisco. Sunday. Contact: Stanley Lesse, M.D., Pres., AAP, 15 W. 81st Street, New York 10024. (212) 873-9233.

May 11-15—**American Psychiatric Association.** Civic Auditorium and Brooks Hall, San Francisco. Monday-Friday. Contact: Robert S. Garber, M.D., Executive Sec., Carrier Clinic, Belle Mead, New Jersey 08502. (201) 359-3101.

May 14-16—**2½ Day Symposium on Mental Health.** UCSF. Thursday-Saturday.

### RADIOLOGY—PATHOLOGY

January 31-Feb. 1—**Los Angeles Radiological Society—22nd Annual Midwinter Radiological Conference.** International Hotel, Los Angeles. Saturday-Sunday. Diagnosis, therapy, and nuclear medicine. \$30. Contact: Arthur F. Schanche, M.D., 8618 So. Sepulveda, Suite 100, Los Angeles 90045.

March 1-6—**American Radium Society.** Hotel del Coronado, Coronado. Sunday-Friday. Uses of radiation and results in treatment of cancer and allied conditions. Contact: John V. Blady, M.D., Secretary, ARS, 2201 Benjamin Franklin Parkway, Philadelphia 19130. (215) 564-4741.

March 3-7—**Diagnostic Radiology.** UCSF. Tuesday-Saturday. Primarily for residents in radiology. Radiological physics, with attention given to the requirements of the American Board of Radiology. 27 hrs.

March 9—**Granulomatous Colitis in Association with Diverticula.** UCSF Department of Radiology and the San Francisco Radiological Society. Monday 8 p.m. Contact: M. B. Ozonoff, M.D., Assistant Prof. of Radiology, UCSF. (415) 648-8200, ext. 414.

April 1-5—**Clinical Cytology for Pathologists.** UCSF at St. Francis Hotel, San Francisco. Wednesday-Sunday. Intensive study in the techniques and interpretation of cytologic specimens. Appropriate separations for the respective fields.

April 17-30—**Radiology of the Gastrointestinal Tract.** USC, Princess Carla Cruise to Mexico from Los Angeles. Two weeks. \$200.

Continuously—**Principles and Clinical Uses of Radioisotopes.** UCSF. Fundamentals for the proper understanding and use of radioactivity in clinical medicine. Training in diagnostic and therapeutic uses of radioisotopes. Normal period of training: 3 months. Two part course: Part A, Basic Fundamentals; Part B, Clinical Applications.

Continuously — **Mammography.** UCSF Mammography Section, Department of Radiology. Three days weekly, beginning with Tuesday. Call several days in advance. Contact: Richard H. Gold, M.D., Mammography Section, Department of Radiology, UCSF. (415) 666-1918.

#### Grand Rounds—Radiology

##### Fridays

Neuroradiology Grand Rounds. 9:30 a.m., Neurology Conference Building 7, V.A. Hospital, Palo Alto, STAN.

#### SURGERY—includes Anesthesiology

January 17-18—**Cadaver Course.** Research Study Club of Los Angeles at USC. Saturday 2-5 p.m.; Sunday 9 a.m.-3 p.m. Surgical Anatomy of the Orbit and Adnexa, Individual Dissection. Limited to 20 applicants attending the Thirty-Ninth Annual Mid-Winter Convention in Ophthalmology and Otolaryngology. \$50. 8 hrs. Contact: Burns C. Steele, M.D., Secretary, Research Study Club of Los Angeles, 1411 W. Olive Ave., Burbank 91506. (213) 846-3614.

January 19-23—**Research Study Club of Los Angeles—39th Annual Mid-Winter Convention in Ophthalmology and Otolaryngology.** Statler Hilton Hotel, Los Angeles. Monday-Friday. Simultaneous lectures in Otolaryngology and Ophthalmology. \$100. 25 hrs. Contact: Burns C. Steele, M.D., Secretary, Research Study Club of Los Angeles, 1411 W. Olive Ave., Burbank 91506. (213) 846-3614.

January 23-25—**Pediatric Anesthesiology—8th Annual Clinical Conference.** Childrens Hospital of Los Angeles. Friday-Sunday. Pre-anesthetic evaluation, methods of induction, choice of agent, pharmacology, iatrogenic diseases, and postoperative care. \$75. 7 hrs. Contact: Wayne Herbert, M.D., Division of Anesthesiology, Childrens Hospital of Los Angeles, P.O. Box 54700, Los Angeles 90054. (213) 663-3341.

January 26-30—**Techniques in Nasal Surgery.** UCLA. Monday-Friday. Observation of dissection of cadaver material and videotaped surgical procedures. Patient selection; photography—pre- and post-operative; facial analysis; basic rhinoplasty; hump removal—lateral and

medial osteotomies; lobule techniques; nasal physiology; surgical techniques; septal surgery; complications of rhinoplasties grafts; trauma—nasal and ear; otoplasties; synthetic injections. \$350. 30 hrs.

February 1-4 — **Surgical Anatomy.** LLU. Sunday-Wednesday. \$150. 32 hrs.

February 7 — **Surgical Emergencies.** PMC. Saturday 8-4:30. Morning session: Monitoring and Management of Shock. Afternoon: Selected and control problems, workshop including case studies and exercises involving blood and gas data, venous pressures. \$40. 8 hrs.

February 7—**Pediatric Urology—The Dilated Ureter; The Uncoordinated Bladder.** See Pediatrics, February 7.

February 25-March 1—**Controversial Areas in Surgery.** UCLA at El Mirador Hotel, Palm Springs. Wednesday-Saturday. Upper intestinal bleeding, treatment of bleeding esophageal varices, pancreatic-duodenectomy, breast cancer surgery, Hirschprung's Disease, toxic megacolon and fulminant colitis, lower gastrointestinal bleeding, pulmonary embolism, organ transplantation, automated multiphasic laboratory screening, recurrent intestinal obstruction, cancer of the rectum, cancer of the thyroid. \$125.

March 13-14—**Surgical Symposium — Changing Concepts in Surgery.** Southern California Permanente Medical Group and Kaiser Foundation Hospitals at Newporter Inn, Newport Beach. Friday-Saturday. Contact: Shirley Gach, Rm. 6014, So. Calif. Permanente Med. Group, 4900 Sunset Blvd., Los Angeles 90027. (213) 663-8411.

March 14-15—**Techniques of Surgery of the Foot.** UCLA. Saturday-Sunday.

March 25-28—**Neurosurgical Society of America.** Ojai Valley Inn, Ojai, Calif. Wednesday-Saturday. Contact: William F. Collins, M.D., Secretary, NSA, 789 Howard Avenue, New Haven, Conn. 06510. (203) 436-1212.

April 8-9 — **Medical Surgical Gastroenterology.** See Medicine, April 8-9.

April 9-10—**General Surgery.** UCSF at St. Francis Hotel, San Francisco. Thursday-Friday.

April 11-12—**Los Angeles County Society of Anesthesiologists—15th Annual Postgraduate Assembly.** Los Angeles Hilton Hotel. Saturday-Sunday. Contact: Los Angeles County Society of Anesthesiologists, 8422 Jamieson Street, Northridge 91324.

#### Grand Rounds—Surgery

##### Wednesdays

7:15 a.m., Auditorium, Kern County General Hospital, Bakersfield. CRMP Area IV.

1st and 3rd Wednesdays. 11:00 a.m., Auditorium, Brown Building, Mount Sinai Hospital, Los Angeles. CRMP Area IV.

##### Thursdays

Neurology and Neurosurgery Grand Rounds. 11:00-12:15. Room 663, Science Building, UCSF.

##### Fridays

1-2:00 p.m., Auditorium, Orange County Medical Center, Orange. UCI.

Neurosurgery. 11:15 a.m., Neurology Conference Building 7, V.A. Hospital, Palo Alto, STAN.



## Saturdays

8:00 a.m., Auditorium, 1st floor, University Hospital of San Diego County, San Diego. UCSD.

9:00 a.m., Room 73-105, Health Sciences Center, UCLA. CRMP Area IV.

8:30 a.m., Assembly Room, Harbor General Hospital, Torrance. CRMP Area IV.

## OF INTEREST TO ALL PHYSICIANS

### CMA Postgraduate Institutes and Circuit Courses

January 24—**West Coast Postgraduate Course, San Luis Obispo.** CMA and UCI at Sierra Vista Hospital and San Luis Obispo General Hospital. Saturday. Enzymes Diagnosis and Thyroid Treatment. \$10. Contact: CMA.

January 29-30 — **Southern Counties Regional Postgraduate Institute.** CMA, STAN, and Southern Counties Medical Societies at El Mirador Hotel, Palm Springs. Thursday-Friday. Thursday a.m.: Acute Injuries of Hands and Face, Acute Cardiac Emergencies and Their Management. Thursday afternoon: The Comatose Patient, Acute Urological Problems. Friday a.m.: Acute Emergencies in the Infant and Child, Shock, Cranial and Spinal Cord Injuries, Acute Pulmonary Problems. Friday afternoon: Symposium on the Multiple Injured Patient. \$20. 12 hrs. Contact: CMA.

February 9, 10, 11-March 2, 3, 4 — **Annual Postgraduate Circuit Courses — Spring Session.** CMA and STAN at Mt. Shasta Community Hospital, Mt. Shasta; Enloe Memorial Hospital, Chico; and Auburn Faith Hospital, Auburn. Radiotherapy and Cancer Management; Depression—Disease and Symptom; Pathology—Past, Present and Future; and Injuries of the Hands and Face. \$20 for Spring Session. Contact: CMA.

April 2-3—**West Coast Counties Regional Postgraduate Institute.** CMA, UCD and Monterey County Medical Society at Del Monte Hyatt House, Monterey. Thursday-Friday. Endocrine Problems with Children (including Diabetes), Infectious Diseases, Cardiac Disease and its Rehabilitation, the Physician and Family Problems. \$20. 11 hrs. Contact: CMA.

May 8-9—**San Joaquin Valley Counties Regional Postgraduate Institute.** CMA, USC, and Fresno County Medical Society at Ahwahnee Hotel, Yosemite. Friday-Saturday. Concurrent symposia in Adolescent Medicine, Coronary Care, Sensitivity Training, and Problems in the Practice of Medicine. \$20. Contact: CMA.

May 15-16 — **Redwood Regional Conference.** CMA, UCSF at Konoti Harbor Inn, Clear Lake. Friday-Saturday. The Anemias and Musculo/Skeletal Conditions in Daily Practice. \$20.

January 15-16—**New and Old Antibiotics.** USC. Thursday-Friday. Geared to the internist, general practitioner, and pediatrician. \$40.

January 19-30—**Intensive Review for Family Practice.** USC. Two weeks. Geared for the individual in general or family practice. Comprehensive review of basic principles, new concepts of disease. \$150.

January 20-April 7—**Psychiatric Principles in a Medical Practice.** See Psychiatry, January 20-April 7.

January 21-23—**Hyperbaric Medicine and Allied Topics.** The Hospital of the Good Samaritan Medical Center, Los Angeles. Wednesday-Friday. Contact: John M. Workman, M.D., Dir., Hyperbaric Unit, The Hospital of the Good Samaritan Medical Center, 1212 Shatto Street, Los Angeles 90017. (213) 482-8111.

January 21-April 29—**Clinical Psychiatry for Non-Psychiatrists: A Course in Medical Psychotherapy.** UCSF. Wednesdays 1-5:00. Open to physicians and paramedical specialists, enrollment limited to 14. Weekly interviews with psychiatric patients, supported by individual hours of faculty consultation and joint treatment reviews of all patients and seminars. Seminars will cover diagnosis and management of psychiatric emergencies, psychiatric illness in children, testing, and community psychiatry. \$25. 60 hrs.

January 25—**What Insurance Is All About, A Symposium for Medical Assistants.** UCSF. Sunday. 5 hrs.

January 26-March 6 — **Mission Orientation Program.** LLU and LLU School of Public Health. Six week program to include tropical medicine, personal health and tropical hygiene, cultural anthropology, practical linguistics, dynamics of interpersonal relationships, seminar discussion by veteran missionaries and others with overseas experience, opportunity to study other areas of personal interest. \$175. Contact: Herschel C. Lamp, M.D., Dir., Mission Orientation Program, School of Public Health, LLU. (714) 796-8333.

January 31-February 1 — **Eighth Scientific Seminar Program.** Memorial Hospital of Southern California, Memorial Hospital of Gardena, and Brotman Foundation of California at Beverly Hilton Hotel, Beverly Hills. Saturday-Sunday. Coma, Adolescent Medicine and Chaos, The Patient with Disordered Blood Coagulation, Arthritis—1970. \$15. Contact: David M. Brotman, M.D., Secretary, Seminar Committee, Memorial Hospital of Southern California, 3828 Hughes Ave., Culver City 90230. (213) 834-3111.

February 6-8—**Financial, Tax, and Investment Planning.** UCLA. Friday-Sunday.

February 6-8—**Drug Abuse.** UCSF at Flamingo Hotel, Santa Rosa. Friday-Sunday. Historical aspects, marijuana, alcoholism, stimulants and depressants, hallucinogens and the psychedelic experience, narcotic addiction, changing patterns of drug abuse, sociological and cultural factors. \$15. 9 hrs.

February 7—**Suicide.** UCSF. Saturday 9-4:30. Degrees of responsibility in suicide; individual, religious, social, legal, and accidental aspects. 6 hrs.

February 7 — **Cardiac Emergencies.** PMC. Saturday. Therapy of intractable heart failure, modern concepts of shock, and emergencies arising in the infant. \$35. 8 hrs.

February 11-12—**Critical Care Medicine and Circulatory Shock.** USC. Wednesday-Thursday. For the general practitioner, internist, general surgeon and surgical specialist. \$50.



February 11-13 — **Course for Physicians in General Practice.** UCSF at Mt. Zion Hospital and Medical Center, San Francisco. Wednesday-Friday. Geriatrics; allergy; endocrinology; cardiovascular topics; pediatrics; elective sessions in anesthesiology, basic electrocardiography, vector approach; rehabilitation in strokes and other neurological diseases; clinical workshops. 20 hrs.

February 12-14—**Conference and Exposition on Electronics in Medicine.** Electronics Management Center in association with the McGraw Hill Publications at Fairmont Hotel, San Francisco. Thursday-Saturday. Contact: James P. Roscow, Electronics/Management Center, New York. (212) 971-6757.

February 15—**Hollywood Community Hospital Annual Symposium.** Sheraton-Universal Hotel, Hollywood. Sunday. Contraceptive and Sexual Problems. Contact: Viola Kindstrand, Symposium Secretary, Hollywood Community Hospital, 6245 de Longpre Ave., Hollywood 90028. (213) 462-2271.

February 15-19—**Loma Linda University School of Medicine, Alumni Association—Postgraduate Convention.** Ambassador Hotel, Los Angeles, and LLU. Sunday-Thursday. Sunday-Monday: Refresher course, LLU. Tuesday-Thursday: Scientific Assembly, Ambassador Hotel. Contact: Samuel H. Fritz, M.D., General Chairman, Alumni Postgraduate Convention for 1970, LLU.

February 26-April 30—**Teaching Clinics in Psychiatry.** See Psychiatry, February 26-April 30.

February 28—**Problems in Social Change Reflected in Medical Practice.** UCSF at Herrick Memorial Hospital, Oakland. Saturday. 6 hrs.

February 28-March 1 — **The Physician and Athletics.** UCSF. Friday-Saturday.

March 7-11—**California Medical Association—Annual Scientific Assembly.** Hilton Hotel, San Francisco. Saturday-Wednesday. General Sessions: Saturday p.m.: Family Practice. Sunday p.m.: Manpower. Monday p.m.: Systems of Delivery. Tuesday p.m.: Birth Defects. Guest Speakers for General Sessions include: Lynn P. Carmichael, M.D., University of Miami School of Medicine; Mike Gorman, National Committee Against Mental Illness; Jerome Pollack, Associate Dean for Medical Care Planning, Harvard Medical School; Henry K. Silver, M.D., Professor of Pediatrics, University of Colorado Medical Center; Eugene A. Stead, Jr., M.D., Duke University Medical Center. Assembly includes special conferences, section meetings, and medical motion picture symposia daily. More complete program listing elsewhere in this issue.

March 19-20 — **Postgraduate Seminar and Clifford Sweet Memorial Lecture.** Childrens Hospital of Oakland. Thursday-Friday. Sex Education for Physicians. Contact: Inetta Carty, Childrens Hospital of Oakland, 51st and Grove Streets, Oakland 94609. (415) 654-5600.

March 21—**Psychiatric Perspectives in Medicine—An Introduction to Family Evaluation and Family In-**

**tervention.** UCSF at Stockton State Hospital, Stockton. Saturday. Principles of family organization, methods of family assessment, demonstration of family interview.

March 25-26 — **Los Angeles County Heart Association and Los Angeles Academy of General Practice—Seventh Annual Spring Symposium for Physicians Practicing General Medicine.** Wednesday-Thursday. Contact: Joe Kennelly, Director, Public Information, LACHA, 2405 W. Eighth Street, Los Angeles 90057. (213) 385-4231.

April 17-18—**Infectious Diseases.** UCSF. See Pediatrics, April 17-18.

April 19—**Office Emergencies: A Symposium for Medical Assistants.** UCSF. Sunday.

April 25-26—**Comparative Medicine.** UCSF. Saturday-Sunday. Professionals in the fields of veterinary medicine, pediatrics, public health and microbiology.

April 25-26—**Sex in Modern Society.** UCSF at Flamingo Motor Hotel, Santa Rosa. Saturday-Sunday.

May 1-2—**Trauma.** UCSF at Mary's Help Hospital, Daly City. Friday-Saturday.

May 3-9—**Hawaii Medical Association.** Hawaiian Village, Honolulu. Sunday-Saturday. Contact: Miss Lee McCaslin, Exec. Sec., HMA, 510 Beretania Street, Honolulu 96813. (808) 536-7702.

Continuously—**Audio-Digest Foundation.** A non-profit subsidiary of CMA. Twice-a-month tape recorded summaries of leading national meetings and surveys of current literature. Services by subscription in: General Practice, Surgery, Internal Medicine, Ob/Gyn, Pediatrics, Anesthesiology, Ophthalmology. Catalog of lectures and panel discussions in all areas of medical practice also available. Contact: Mr. Claron L. Oakley, Editor, 619 S. Westlake Ave., Los Angeles 90057.

## TELEVISION

**Southern California's Medical Television Network.** UCLA. Weekly broadcasts, Tuesdays 8:30 a.m. Contact: UCLA Medical Television Network. (213) 825-1341.

January 20—**Post Hospital Care of the Cancer Patient.** UCLA and City of Hope National Medical Center.

January 27—**Placebos.** University of Western Ontario, Canada.

February 3—**The Transient Ischemic Stroke.** UCLA and CRMP Area I.

February 10—**Rheumatoid Arthritis.** British Broadcasting Company.

February 17—**Venereal Disease.** UCLA School of Medicine.

February 24—**Allergy Report.** University of Western Ontario, Canada.

# 99th annual session program



***SAN FRANCISCO HILTON HOTEL***

***MARCH 7 to 11, 1970***

SCIENTIFIC SESSIONS • TECHNICAL AND SCIENTIFIC EXHIBITS  
MOTION PICTURE SYMPOSIA • MEETINGS OF THE  
HOUSE OF DELEGATES

**california medical association**

# CALIFORNIA MEDICAL ASSOCIATION ANNUAL MEETING

March 7 to 11, 1970, San Francisco

## Daily Schedule of Scientific Sessions

Unless otherwise stated, all meeting rooms listed in the programs are in the San Francisco Hilton Hotel

<p><b>SATURDAY, MARCH 7 MORNING MEETINGS</b></p> <p>Section Meetings:</p> <p>Industrial Medicine and Surgery, and Orthopedics ALL DAY</p> <p>Internal Medicine</p> <p>Orthopedics, and Industrial Medicine and Surgery ALL DAY</p> <p>Pathology</p> <p>Psychiatry and Neurology ALL DAY</p> <p>Special Conferences:</p> <p>Cancer Symposium ALL DAY</p> <p>Radiology Conference ALL DAY</p> <p>American College of Chest Physicians, California Chapter ALL DAY</p> <p>California Society of Anesthesiologists ALL DAY</p> <p>California Society of Medical Assistant Instructors ALL DAY</p> <p>Scientific Exhibit Opening 12 Noon</p> <p><b>AFTERNOON MEETINGS</b></p> <p><b>CMA HOUSE OF DELEGATES — Opening Session (4:00 p.m.)</b></p> <p>General Meeting: What is Family Practice?</p> <p>California Society of Pathologists</p>	<p><b>MONDAY, MARCH 9 MORNING MEETINGS</b></p> <p>Section Meetings:</p> <p>Internal Medicine</p> <p>Obstetrics and Gynecology ALL DAY</p> <p>Pathology and Urology</p> <p>Urology ALL DAY</p> <p>Special Conferences:</p> <p>Alcohol and Drugs</p> <p>Confronting the Teenager</p> <p>Emergency and Disaster Preparedness ALL DAY</p> <p>New Roles in Nursing</p> <p>American College of Obstetrics and Gynecology, California Division Luncheon (12:00 noon)</p> <p>California Academy of Pediatrics, Chapter I Luncheon (12:00 noon)</p> <p>Scientific Exhibit ALL DAY</p> <p><b>MOTION PICTURE PROGRAM: Pediatrics</b></p> <p><b>AFTERNOON MEETINGS</b></p> <p>General Meeting: Systems of Delivery of Medical Care</p> <p>Section Meetings:</p> <p>Pediatrics</p> <p>Preventive Medicine and Public Health</p> <p>Special Conferences:</p> <p>Prevention of Coronary Artery Disease in Industry</p> <p>California Academy of Preventive Medicine Dinner (7:00 p.m.)</p> <p><b>MOTION PICTURE PROGRAM: Practical Problems in Surgery</b></p>
<p><b>SUNDAY, MARCH 8 MORNING MEETINGS</b></p> <p>Section Meetings:</p> <p>Allergy ALL DAY</p> <p>Anesthesiology ALL DAY</p> <p>Dermatology</p> <p>General Practice and Pediatrics</p> <p>Internal Medicine</p> <p>Otolaryngology</p> <p>Pediatrics and General Practice</p> <p>Plastic Surgery ALL DAY</p> <p>Radiology</p> <p>Special Conferences:</p> <p>Pathology Conference ALL DAY</p> <p>Scientific Exhibit ALL DAY</p> <p><b>AFTERNOON MEETINGS</b></p> <p>General Meeting: What Is the Assistant to the Physician?</p> <p>Section Meetings:</p> <p>Ophthalmology</p> <p>Physical Medicine</p> <p>Special Conferences:</p> <p>L. Henry Garland Memorial Lecture</p> <p>California Radiological Society</p> <p><b>MOTION PICTURE PROGRAM: Surgery</b></p>	<p><b>TUESDAY, MARCH 10 MORNING MEETINGS</b></p> <p>Section Meetings:</p> <p>General Practice ALL DAY</p> <p>General Surgery ALL DAY</p> <p>Special Conferences:</p> <p>California Medical Assistants Association</p> <p>Medical Aspects of High School Sports</p> <p>Symposium on Environmental Health</p> <p>Scientific Exhibit ALL DAY</p> <p><b>MOTION PICTURE PROGRAM: Medicine</b></p> <p><b>AFTERNOON MEETINGS</b></p> <p><b>HOUSE OF DELEGATES (3:00 p.m.)</b></p> <p>Special Conferences:</p> <p>Birth Defects</p> <p><b>MOTION PICTURE PROGRAM: Drug Abuse</b></p> <p><b>WEDNESDAY, MARCH 11 MORNING MEETINGS</b></p> <p><b>HOUSE OF DELEGATES (9:00 a.m.)</b></p> <p>Will continue until business is completed</p> <p>Scientific Exhibit (Until Noon)</p>



# Scientific Program

CALIFORNIA  
MEDICAL  
ASSOCIATION

## Ninety-Ninth Annual Session

San Francisco  
Hilton Hotel

SAN FRANCISCO  
March 7 to 11, 1970

HOUSE OF DELEGATES  
OPENING MEETING  
SATURDAY, MARCH 7  
4:00 P.M.

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# Information

**BADGES**—It is important that badges be worn at all times. Admission to scientific meetings is by badge only.

**COUNCIL**—The Council will meet Friday, March 6, 4 p.m., and Saturday, March 7, 9 a.m. to noon. Rooms will be posted on the hotel schedule boards.

**HOUSE OF DELEGATES**—For list of delegates and alternates, meeting times, places and agenda, see pages 25 to 30.

**EMERGENCY CALLS AND MESSAGES**—Convention Emergency Call Number (415) 776-1390 from 8 a.m. to 5 p.m., Saturday, March 7, through Wednesday, March 11.

**MESSAGE CENTER (415-776-1390)**—Provided through the courtesy of the Pacific Telephone Company — Registration Desk, East Lounge, Ballroom Floor — Registration Desk is open from 8 a.m. to 5 p.m. — The Association will attempt to transmit emergency messages to the individual physician. Each physician should notify his own office of the exact times and meetings he plans to attend, and the convention number. Routine messages will be kept at the Message Center in the East Lounge, Ballroom Floor, at the entrance to the exhibit area and adjacent to the Registration Desk. Physicians are requested to check with the Message Center at least once a day.

**INDEX TO PARTICIPANTS**—See pages 8 and 9.

**MOTION PICTURE SYMPOSIA** will be shown in the Garden Room, Ballroom Floor. See page 23.

**SCIENTIFIC AND ORGANIZATIONAL EXHIBITS** — Ballroom Floor, California Room. See page 24.

**TECHNICAL EXHIBITS**—Ballroom Floor, Continental Parlors 6, 7, 8, 9, and in the North, East and South Lounges. See pages 38 to 42.

**REGISTRATION AND INFORMATION**—Registration and information desks are located in the East Lounge, Ballroom Floor, at the entrance to the exhibit area. All members, guests and visitors are requested to register immediately upon arrival. There is no charge for registration. Registration desks are open Saturday through Wednesday. Admission to the general and section sessions, and exhibit areas is by badge only.

Members wishing to vote in specialty sections must indicate appropriate section when registering; voting in other sections will not be allowed.

**QUALIFICATIONS/REQUIREMENTS FOR REGISTRATION**—(a) All M.D.s with credentials showing that they hold valid license to practice medicine. (Membership card in C.M.A.; county medical society/association or A.M.A. membership card.) (b) Medical students will be admitted upon presentation of credentials from their medical schools identifying them as medical students. (A membership card of the Student American Medical Association or letter from their dean's office.) (c) Medical Assistants will be admitted upon presentation of a letter from the physician-employer or C.M.A.A. membership card. (d) Military paramedical personnel will be admitted upon presentation of a letter requesting their admittance, written by their commanding officer. (e) Dentists (D.D.S.), doctors of veterinary medicine (D.V.M.), registered nurses (R.N.), student nurses, x-ray technicians, laboratory technicians, allied public health personnel, and others will be admitted provided they have proper identification. (f) All questions on admission will be passed upon by a member of the Committee on Registration who will be present at the desk.

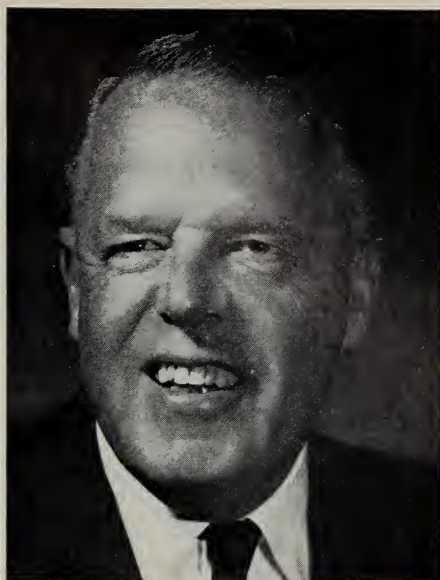
## ACKNOWLEDGMENT

ONCE AGAIN an educational program of considerable merit has been developed through the combined effort of many individuals acting for their Sections with the assistance of Specialty Societies and the Medical Schools of the State.

The Committee on Scientific Assemblies would be helpless without the assistance and interest of many dedicated individuals and acknowledges their contribution and efforts in the development of this program which we believe is again a step forward.

JOHN B. DILLON, M.D., *Chairman*  
Committee on Scientific Assemblies  
of the Scientific Board

# CALIFORNIA MEDICAL ASSOCIATION



ALBERT G. MILLER, *President*



RALPH W. BURNETT, *President-Elect*



# Guest Speakers



LYNN P. CARMICHAEL



MIKE GORMAN



HENRY K. SILVER



EUGENE A. STEAD, JR.

- LYNN P. CARMICHAEL, M.D., Miami—Director, Division of Family Medicine, University of Miami School of Medicine.
- MIKE GORMAN, Washington, D.C.—Executive Director, National Committee Against Mental Illness.
- JEROME POLLACK, B.S., Boston—Associate Dean of the Economics of Medical Care, Harvard Medical School; Executive Director, Harvard Community Health Plan, Inc. (Not pictured.)
- HENRY K. SILVER, M.D., Denver—Professor of Pediatrics, University of Colorado Medical Center.
- EUGENE A. STEAD, JR., M.D., Durham, N.C.—Professor of Medicine, Duke University.

# OUT-OF STATE GUESTS OF SECTIONS AND ORGANIZATIONS

## • *Anesthesiology*

JOSEPH J. BUCKLEY, M.D., Minneapolis. Professor of Anesthesiology, University of Minnesota Medical School.

## • *Dermatology*

ROBERT J. GORLIN, D.D.S., M.S., Minneapolis. Professor and Chairman, Division of Oral Pathology, University of Minnesota School of Dentistry.

## • *General Practice*

HAROLD T. CONRAD, M.D., Lexington. Director Clinic Research Center.

## • *Obstetrics and Gynecology*

ROBERT W. KISTNER, M.D., Boston. Assistant Clinical Professor of Obstetrics and Gynecology, Harvard Medical School.

## • *Pathology*

JON V. STRAUMFJORD, JR., M.D., Ph.D., Birmingham. Professor and Chairman, Department of Clinical Pathology; and Clinical Pathologist in Chief, University Hospital, University of Alabama.

MARIO WERNER, M.D., St. Louis. Washington University School of Medicine.

## • *Pediatrics and General Practice*

HEINZ F. EICHENWALD, M.D., Dallas. Professor of Pediatrics, University of Texas, Southwestern Medical School.

## • *Psychiatry and Neurology*

CHARLES W. SOCARIDES, M.D., New York City. Assistant Clinical Professor of Psychiatry, Albert Einstein College of Medicine.

## • *Radiology*

WILLIAM CAMPBELL, M.D., D.M.R.D., East Grinstead, Sussex, England. The Queen Victoria Hospital, Plastic Surgery and Joint Injuries Centre.

W. PETER COCKSHOT, M.D., Hamilton, Ontario, Canada. Professor and Chairman, Department of Radiology, Chedoke Hospital, McMaster University.

JACK EDEIKEN, M.D., Philadelphia. Department of Radiology, Thomas Jefferson University Hospital.

RICHARD H. MARSHAK, M.D., New York City. Attendant Radiologist, Mount Sinai Hospital.

M. J. RAPHAEL, M.B., London, England. Department of Radiology, Postgraduate Medical School.

JOSEF RÖSCH, M.D., Prague, Czechoslovakia. Charles University.

## • *Urology*

FRANK J. LEARY, M.D., Rochester, Minn. Mayo Clinic.

## • *California Medical Association*

*California Division, and Alameda, Contra Costa, Marin, San Francisco, San Mateo, and Santa Clara branches, American Cancer Society*

ALFRED W. KOFF, M.D., New York City. Professor, Department of Dermatology, New York University School of Medicine; and Head, Oncology Section, Skin and Cancer Unit, New York University Medical Center.

## • *California Medical Association*

*California Heart Association*

ROBERT A. BRUCE, M.D., Seattle. Department of Medicine, University of Washington School of Medicine.

WILLIAM B. KANNEL, M.D., Framingham, Mass. Director, Framingham Heart Study.

## • *California Medical Association*

*California Nurses' Association*

DARREL J. MASE, Ph.D., Gainesville, Fla. Dean, College of Health Related Professions, University of Miami.

## • *California Radiological Society*

*L. Henry Garland Memorial Lecture*

MELVIN P. JUDKINS, M.D., Portland. Professor of Radiology; and Director, Cardiovascular Laboratories, University of Oregon Medical School.

## • *California Medical Association*

*Committee on Cancer*

J. BEACH HAZARD, M.D., Cleveland. Chairman, Division of Pathology, Cleveland Clinic.

## • *The National Foundation—March of Dimes*

HENRY L. NADLER, M.D., Chicago. Head, Division of Genetics, Children's Memorial Hospital; and Associate Professor of Pediatrics, Northwestern School of Medicine.

# INDEX TO PARTICIPANTS

## PARTICIPANTS FROM OUT OF STATE

Bruce, Robert A., Seattle	12	Cockshott, W. Peter, Hamilton, Ontario	2
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Carmichael, Lynn P., Miami	14, 16	Comarr, A. Estlin, Long Beach	2
Campbell, William, East Grinstead, England	21	Conrad, Harold T., Lexington, Ky.	1
Cockshott, W. Peter, Hamilton, Ontario	21	Cox, Robert S., Jr., San Jose	1
Conrad, Harold T., Lexington, Ky.	16	Crisp, James R., III, San Francisco	1
Edeiken, Jack, Philadelphia	21	Cross, Carroll E., Davis	1
Eichenwald, Heinz F., Dallas	16, 20	David, Joseph S., Orange	1
Gorlin, Robert J., Minneapolis	16	Deissler, Karl J., Oakland	1
Gorman, Mike, Washington, D.C.	14	Denson, Judson S., Los Angeles	1
Hazard, J. Beach, Cleveland	10, 19	DeTornyay, Rheba, San Francisco	1
Judkins, Melvin P., Portland	10, 21	Diamond, Bernard L., Berkeley	2
Kannel, William B., Framingham, Mass.	12	Dillon, John B., Los Angeles	1
Kistner, Robert W., Brookline, Mass.	18	Dowdy, Andrew H., Los Angeles	2
Kopf, Alfred W., New York City	10	Dreyfus, Pierre M., Davis	2
Leary, Frank J., Rochester, Minn.	22	Edeiken, Jack, Philadelphia	2
Marshak, Richard H., New York City	21	Eichenwald, Heinz F., Dallas	16, 2
Mase, Darrel J., Gainesville, Fla.	12	Epstein, Charles J., San Francisco	1
Nadler, Henry L., Chicago	13	Epstein, John H., San Francisco	1
Pollack, Jerome, Boston	14	Erskine, John M., San Francisco	2
Raphael, M. J., London, England	21	Farr, Lee E., Berkeley	1
Rösch, Josef, Prague, Czechoslovakia	21	Fischer, Vernon, San Jose	1
Silver, Henry K., Denver	14	Forsham, Peter H., San Francisco	1
Socarides, Charles W., New York City	21	Freedman, Robert I., Los Angeles	1
Stead, Eugene A., Jr., Durham, N.C.	14	Freedman, Walter J., Berkeley	2
Straumfjord, Jon V., Jr., Birmingham, Ala.	19	Friedman, M. Wallace, San Francisco	1
Werner, Mario, St. Louis	19	Fung, Wayne E., San Francisco	1
Amsterdam, Ezra A., Davis	17	Galant, Stanley, San Francisco	1
Anderson, Gail V., Los Angeles	18	Gardner, Richard E., San Francisco	2
Andrus, L. H., King City	14	Gettelman, Eugene, Encino	20, 2
Asbury, Arthur K., San Francisco	21	Gibson, Count D., Jr., Stanford	1
Ashburn, William L., San Diego	21	Gillanders, William, San Francisco	12, 1
Austin, Glenn E., Los Altos	14	Gittes, R. F., San Diego	19, 2
Baer, Louis S., Burlingame	20	Gobar, Robert F., Daly City	1
Barger, James H., Olive View	21	Goebel, James L., Ross	2
Bauer, Robert O., Los Angeles	18	Goldberg, Marshall G., Encino	1
Benis, Max, Los Angeles	15	Goode, Richard L., Stanford	1
Bennett, Leslie R., Los Angeles	21	Gorlin, Robert J., Minneapolis	1
Blum, Henrik L., Berkeley	20	Gorman, Mike, Washington, D.C.	1
Bolt, Robert J., Davis	17	Gozzi, Ethel, King City	1
Bookman, Ralph, Beverly Hills	15	Graves, William K., San Francisco	1
Bostick, Warren L., Irvine	12	Gray, Gary M., Stanford	1
Brenner, Paul H., Solana Beach	18	Griffeath, Harold I., San Francisco	1
Brodsky, Carroll M., San Francisco	20	Grossman, Moses, San Francisco	2
Brown, Reynold F., San Francisco	10, 21	Haglund, Elizabeth, San Francisco	1
Bruce, Robert A., Seattle	12	Hamilton, Constance B., Downey	1
Buckley, Joseph J., Minneapolis	15	Hamilton, William K., San Francisco	1
Bullock, Joseph D., San Francisco	15	Harvey, Birt, Palo Alto	1
Bunker, John P., Palo Alto	15	Hatoff, Alexander, Oakland	2
Burnett, Ralph W., Bakersfield	14	Havel, Richard J., San Francisco	1
Burrill, Clarence W., Jr., Westminster	16, 23	Hazard, J. Beach, Cleveland	10, 1
Caillouette, James C., Pasadena	18	Helsper, James, Pasadena	1
Call, Richard W., Los Angeles	12	Henderson, Charles C., San Mateo	1
Campbell, William, East Grinstead, England	21	Hetherington, John, Jr., San Francisco	1
Carman, Charles T., San Francisco	15	Hicks, Shelby M., Merced	2
Carmichael, Lynn P., Miami	14, 16	Hockwald, Robert S., San Francisco	1
Carson, Merl J., Orange	13	Hodgman, Joan E., Los Angeles	1
Chambers, Van Vleck, Palo Alto	20	Hofmann, William W., Palo Alto	2
Chappell, Clifford C., Berkeley	18	Hollister, Leo E., Stanford	1
Chesbro, Wayne P., Berkeley	11	Holman, Halsted R., Stanford	1



Jacobs, Alvin H., Stanford	16	Overstreet, Edmund W., San Francisco	18
Jenkins, Edward R., Elk Grove	11	Oyler, Robert H., Claremont	16
Judkins, Melvin P., Portland	10, 21		
Kannel, William B., Framingham, Mass.	12	Patton, Robert G., San Francisco	23
Kattus, Albert A., Jr., Los Angeles	12	Payton, Charles, San Francisco	14
Katz, Alfred D., Los Angeles	19	Peck, Sam, San Diego	22
Kay, Harold, Oakland	22	Pierce, Max K., Los Angeles	15
Kaye, Ronald L., Palo Alto	23	Pollack, Jerome, Boston	14
Kern, William H., Los Angeles	19, 22	Pomer, Sydney L., Los Angeles	21
King, Eileen B., San Francisco	19, 22	Prince, David A., Stanford	17
Kistner, Robert W., Brookline, Mass.	18		
Koegler, Ronald R., Los Angeles	21	Raphael, M. J., London, England	21
Kolb, Felix O., San Francisco	17	Raskin, Neil H., San Francisco	21
Kopf, Alfred W., New York City	10	Reaven, Gerald M., Stanford	17
Kramer, John C., Irvine	16	Reid, Robert H., Los Gatos	10
		Reider, Norman, San Francisco	21
La Dou, Joseph, Palo Alto	19	Reynolds, Telfer B., Los Angeles	15
Langdon, Edward A., Los Angeles	14	Robertson, Jack R., Santa Maria	18
Larson, Roger K., Fresno	14	Rösch, Josef, Prague, Czechoslovakia	21
Leary, Frank J., Rochester, Minn.	22	Rubin, David, Los Angeles	20
Lee, Philip R., San Francisco	20	Rubin, Henry J., Beverly Hills	20
Leonards, Richard, San Francisco	23	Rubinstein, Morton K., Los Angeles	21
Levy, Steven E., Sherman Oaks	15		
Lipson, Leon W., Stanford	19	Saylor, Louis F., Berkeley	20
Lodge, J. Philip, San Bernardino	14	Schneidman, Harold M., San Francisco	16
Long, Albert E., San Francisco	11	Schweitzer, Robert J., Oakland	10
Longley, Jay R., Newport Beach	22	Scott, Alan B., San Francisco	18
Lyons, Thomas W., La Mesa	11	Shanbrom, Edward, Santa Ana	13
		Shepard, Richard A., Oakland	10
Maltz, Robert, Stanford	19	Silver, Henry K., Denver	14
Marks, Jerome, San Francisco	13	Silverman, William A., San Francisco	16, 20
Marsh, Earle, San Francisco	12	Simmons, Daniel H., Los Angeles	15
Marshak, Richard H., New York City	21	Sleisinger, Marvin H., San Francisco	17
Mase, Darrel J., Gainesville, Fla.	12	Smith, David E., San Francisco	17
McBride, J. P., Los Angeles	18	Smith, Lloyd H., Jr., San Francisco	17
McDevitt, Hugh O., Stanford	17	Socarides, Charles W., New York City	21
McDonnel, Gerald M., Los Angeles	10	Spann, James F., Jr., Davis	17
MacFarland, Philip M., Santa Ana	12	Stead, Eugene A., Jr., Durham, N.C.	14
McLarty, William, Berkeley	11	Stevens, William, Salinas	11
McNally, John T., Stockton	11	Straumfjord, Jon V., Jr., Birmingham, Ala.	19
Milligan, Robert G., San Francisco	20	Strick, Lawrence, Encino	15
Mims, Matlock M., Los Angeles	19, 22	Sumner, Ruth, San Francisco	14
Mintz, Frederic, San Francisco	12		
Muldavin, Michael S., Berkeley	19	Tolls, R. Eugene, San Francisco	19
Murray, John F., San Francisco	17	Tooley, William H., San Francisco	16, 20
		Ungerleider, J. Thomas, Los Angeles	16
Nadler, Henry L., Chicago	13		
Nichaman, Milton Z., San Francisco	12	Vaeth, Jerome M., San Francisco	10
Noble, W. Morris H., San Francisco	23		
Northway, William H., Jr., Palo Alto	21	Werner, Mario, St. Louis	19
Novak, Frank J., Stanford	19	Wiggins, Howell E., San Diego	11
Ovey, Harold S., Whittier	15	Willet, David E., San Francisco	14
Oyhan, William L., San Diego	13	Wilson, Archie F., Los Angeles	15
		Winer, Julius H., Beverly Hills	22
		Wiseman, Daniel H., Van Nuys	15
Ph, William, Torrance	16, 20		
Rnstein, Walter, La Jolla	16	Yoell, John H., Los Angeles	19
Toole, John S., Riverside	15	Zelis, Robert F., Davis	17

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# *special conferences*

**SATURDAY, MARCH 7** 9:30 a.m. to 5:00 p.m.—Italian Room  
St. Francis Hotel, Union Square

## **RADIOLOGY CONFERENCE**

*Committee on Cancer, California Medical Association*

Chairman: Gerald M. McDonnell, M.D., Los Angeles  
Secretary: Robert H. Reid, M.D., Los Gatos

9:30 a.m. to 12:00 noon—**THERAPY SESSION**

1:30 p.m. to 3:30 p.m.—**DIAGNOSTIC SESSION**

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**SATURDAY, MARCH 7** 2:00 p.m.—Continental Parlor #4

## **FOURTH ANNUAL CANCER SYMPOSIUM** **TOPIC OF CANCER: ONLY SKIN DEEP**

*Sponsored Jointly by the California Medical Association  
and the California Division, and the Alameda, Contra  
Costa, Marin, San Francisco, San Mateo, and Santa Clara  
Branches of the American Cancer Society*

Chairman: Robert J. Schweitzer, M.D., Oakland

2:00—Welcome—Robert J. Schweitzer, M.D., Oakland, President,  
Alameda Branch, American Cancer Society

2:05—Clinical Manifestations of Skin Cancer—Alfred W.  
Kopf, M.D., New York City, by invitation

2:35—Recognition and Management of Pre-malignant Skin Lesions,  
Use of Liquid Nitrogen and Topical 5-FU—James Helsper, M.D., Pasadena

2:55—Sunshine and Skin Cancer—Epidemiology and Etiology—  
John H. Epstein, M.D., San Francisco

3:25—Recess

3:35—Radiation Therapy of Skin Cancer—Jerome M. Vaeth, M.D., San Francisco

3:55—Chemosurgery and Surgical Management of Skin Cancer—  
Richard A. Shepard, M.D., Oakland

4:30—Questions and Answers Session

**SUNDAY, MARCH 8**

9:00 a.m. to 5:30 p.m.  
—Continental Parlor #4

## **PATHOLOGY CONFERENCE**

*Committee on Cancer, California Medical Association*

### **Tumors of the Thyroid**

Moderator: J. Beach Hazard, M.D., Cleveland, by invitation

9:00 a.m. to 12:30 p.m.—2:00 p.m. to 5:30 p.m.

The registration fee for this Conference is \$30.00, which includes attendance, a set of 25 slides, protocol and addenda. For attendance only, the fee is \$15.00. There is no charge for residents and interns. Those wishing to attend are requested to register with Weldon K. Bullock, M.D., Executive Director, Tumor Tissue Registry, CMA Committee on Cancer, Los Angeles County—University of Southern California Medical Center, 1200 North State Street, Los Angeles 90033.

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**SUNDAY, MARCH 8**

2:00 p.m.—Italian Room  
St. Francis Hotel, Union Square

## **Fourth Annual** **L. HENRY GARLAND** **MEMORIAL LECTURE**

*Sponsored by the California Radiological Society*

2:00—Introduction—Reynold F. Brown, M.D., San Francisco, President, California Radiological Society

2:05—A Breakthrough in the Battle with Coronary Artery Obstructive Disease—Melvin P. Judkins, M.D., Portland, Ore., by invitation

3:00—Recess

3:15—Annual Meeting—California Radiological Society

MONDAY, MARCH 9 9:00 a.m.—Continental Parlor #2

## ALCOHOL AND DRUGS

### Symposium

*Committee on Dangerous Drugs and  
Committee on Alcoholism,  
California Medical Association*

Program and Speakers to be announced

MONDAY, MARCH 9 9:00 a.m.—Walnut Suite

## CONFRONTING THE TEENAGER

*Committee on Medicine and Religion,  
California Medical Association*

Chairman: Albert E. Long, M.D., San Francisco

9:00—Confronting the Teenager:

Drugs  
Personal Relationships  
Confidentiality

Speakers to be announced

10:00—Recess

10:15—Panel Discussion—Questions and Answers Session

Members of the Panel: To be announced

MONDAY, MARCH 9 9:00 a.m.—Continental Parlor #1

## EMERGENCY AND DISASTER PREPAREDNESS

### Symposium

*Commission on Community Health Services,  
Committee on Automotive and Traffic Safety,  
Committee on Disaster Medical Care,  
Committee on Emergency Medical Care,  
California Medical Association*

Chairman: John T. McNally, M.D., Stockton

9:00—Introduction—Speaker to be announced

9:10—**Emergency Medical Care:  
Initial Considerations**

### PANEL DISCUSSION I

Moderator: Howell E. Wiggins, M.D., San Diego

9:10—1. Forces and Stress Concerned in Auto Trauma Due to Collision

2. Extrication of the Injured from the Wrecked Vehicle

3. Emergency Medical Care at the Accident Site

Speakers to be announced

10:15—Questions and Answers Session

11:00—**Emergency Medical Care:  
Support Facilities**

### PANEL DISCUSSION II

Moderator: Charles C. Henderson, M.D., San Mateo

11:00—1. The Role of the Ambulance Attendant—William Stevens, Salinas, by invitation

2. Transportation of the Injured—Edward R. Jenkins, M.D., Elk Grove

3. Emergency Communications—William McLarty, Berkeley, by invitation

4. Emergency Room: Physician-Nurse Coordination and Care—Thomas W. Lyons, M.D., La Mesa

12:15—Questions and Answers Session

MONDAY, MARCH 9 2:00 p.m.—Continental Parlor #1

## SYMPOSIUM ON EMERGENCY AND DISASTER PREPAREDNESS (Continued)

**Civil Disturbance: Student Unrest in Berkeley and the  
Problem of Disaster Medical Care**

2:00—Organization and Planning in Disaster Medical Care—  
Speaker to be announced

2:15—**The Support City Hospitals**

### PANEL DISCUSSION III

Moderator: Wayne P. Chesbro, M.D., Berkeley

2:15—1. Herrick Hospital

2. Cowell Hospital

3. Alta Bates Hospital

4. Highland Hospital

5. Student Physicians

6. Medical Committee for Human Rights

7. Regional Medical Support—Lee E. Farr, M.D., Berkeley

Speakers to be announced

4:20—Questions and Answers Session

4:35—Summary and Closing Statement—John T. McNally, M.D., Stockton



MONDAY, MARCH 9

9:30 a.m.—Continental Parlor #5

## NEW ROLES IN NURSING—OR THE PROBLEMS OF PARANURSING PERSONNEL

*Sponsored Jointly by the California Medical Association and the California Nurses' Association*

Moderator: Warren L. Bostick, M.D., Irvine

9:30—The Changing Role of the Nurse: What is the Health Team? Who is the Captain? Who is the Coach? What's the Game?—Darrel J. Mase, Ph.D., Gainesville, Fla., by invitation

10:00—Questions from the Audience and Reactor Panel

Members of the Reactor Panel: Rheba DeTornay, R.N., Ph.D., San Francisco, President-Elect, California Nurses' Association, by invitation; Earle Marsh, M.D., Co-ordinator, Allied Health Professions, University of California School of Medicine, San Francisco; William Gillanders, representing SAMA, San Francisco, by invitation; Vernon Fischer, President, Student Nurses Association of California, San Jose, by invitation.

10:15—Do We Need New Roles or New Nurses, or Both?—Constance B. Hamilton, R.N., Research Associate, Department of Nursing, Rancho Los Amigos Hospital, Downey, by invitation

10:45—Questions from the Audience and Reactor Panel

Members of the Reactor Panel: As listed above

11:00—The Changing Roles of the Physician and Nurse in Coronary Care Units — Harold I. Griffeath, M.D., Chairman, California Medical Association Committee on Cardiovascular Diseases, San Francisco

11:30—Questions from the Audience and Reactor Panel

Members of the Reactor Panel: As listed above

MONDAY, MARCH 9

1:30 p.m.—Continental Parlor #2

## THE PREVENTION OF CORONARY ARTERY DISEASE IN INDUSTRY

### Symposium

*Sponsored Jointly by the California Heart Association and the Committees on Occupational Health and Cardiovascular Diseases, California Medical Association*

Chairman: Robert S. Hockwald, M.D., San Francisco

1:30—Introduction—Robert S. Hockwald, M.D., San Francisco, Chairman, American Heart Association Committee on Stress, Strain and Heart Disease

1:40—Risk Factors and Screening—

Introduction—Milton Z. Nichaman, M.D., San Francisco, by invitation.

Speaker—William B. Kannel, M.D., Framingham, Mass., by invitation.

2:15—Stress Testing in the Diagnosis of Coronary Artery Disease—

Introduction—Harold I. Griffeath, M.D., San Francisco.

Speaker—Robert A. Bruce, M.D., Seattle, by invitation.

3:00—Exercise Therapy and Its Rationale in Coronary Artery Disease—

Introduction—Robert S. Hockwald, M.D., San Francisco.

Speaker—Albert A. Kattus, Jr., M.D., Los Angeles.

3:30— PANEL DISCUSSION

Members of the Panel: Robert A. Bruce, M.D., Seattle, by invitation; Richard W. Call, M.D., Los Angeles; Harold I. Griffeath, M.D., San Francisco; Robert S. Hockwald, M.D., San Francisco; William B. Kannel, M.D., Framingham, Mass., by invitation; Albert A. Kattus, Jr., Los Angeles; and Frederic Mintz, M.D., San Francisco.

TUESDAY, MARCH 10

9:00 a.m.—Teakwood Suite

## MEDICAL ASPECTS OF HIGH SCHOOL SPORTS Symposium

*Committee on the Medical Aspects of Sports and Physical Fitness, California Medical Association*

Chairman: Philip M. McFarland, M.D., Santa Ana

9:00—Competitive Athletics and Their Effect on Teenage Health

9:30—New Concepts in the Prevention and Treatment of Traumatic and Symptomatic Disorders Related to Sports

9:45—Relating the Private Patient's Symptoms to His Athletic Involvements

10:00—Panel Discussion

10:45—The Physician and His Patient: The Physician is Involved

11:00—Medical Societies and Community Needs

11:30—Questions and Answers Session

Speakers to be announced

TUESDAY, MARCH 10 9:00 a.m.—Walnut Suite

**SYMPOSIUM ON ENVIRONMENTAL  
HEALTH**

*Committee on Environmental Health,  
California Medical Association*

Program to be announced

TUESDAY, MARCH 10 10:00 a.m.—Continental Parlor #1

**CALIFORNIA MEDICAL ASSISTANTS  
ASSOCIATION**

10:00—Tax Advantages of Incorporating a Professional Medical  
Practice—Jerome Marks, A.B., J.D., LL.M., San Fran-  
cisco, by invitation

Program to be announced

TUESDAY, MARCH 10 1:30 p.m.—Continental Parlor #5

**BIRTH DEFECTS**

*National Foundation—March of Dimes,  
Medical Advisory Committees, California Chapters*

Moderator: Merl J. Carson, M.D., Orange

1:30—Amniocentesis in Diagnosis of Genetic Defects—Henry  
L. Nadler, M.D., Chicago, by invitation

2:10—Metabolic Errors and Birth Defects—William L. Nyhan,  
M.D., La Jolla, by invitation

2:50—Profile Screening in the Laboratory of Congenital De-  
fects in the Newborn—Edward Shanbrom, M.D., Los  
Angeles

3:10—Recess

3:25— **Surgical Management of Birth  
Defects by the Pediatric Surgeon**

PANEL DISCUSSION

Moderator: Joseph S. David, M.D., Orange

A discussion of indications and techniques for emergency  
and elective surgical procedures in patients with con-  
genital defects.

Members of the Panel: Henry L. Nadler, M.D., Chicago, by  
invitation; William L. Nyhan, M.D., San Diego, by  
invitation; and Edward Shanbrom, M.D., Los Angeles.

# Scientific Sessions

## GENERAL MEETINGS

### FIRST GENERAL MEETING

SATURDAY, MARCH 7 1:30 p.m.—Continental Parlor #5

#### What Is Family Practice?

Moderator: Roger K. Larson, M.D., Fresno

1:30—Introduction—Roger K. Larson, M.D., Fresno

1:40—The Role of the Family Physician—Lynn P. Carmichael, M.D., Miami, by invitation

2:10—The Hospital's Role in Training the Family Physician Specialist—J. Philip Loge, M.D., San Bernardino

2:40—Family Practice from the Medical Student's Viewpoint—Charles Payton, San Francisco, by invitation

3:10—Integration of Family Practice in the Traditional School Curriculum—Edward A. Langdon, M.D., Los Angeles

3:40— PANEL DISCUSSION

Members of the Panel: Lynn P. Carmichael, M.D., Miami, and Eugene A. Stead, Jr., M.D., Durham, both by invitation; Edward A. Langdon, M.D., Los Angeles; J. Philip Loge, M.D., San Bernardino; and Charles Payton, San Francisco, by invitation.

### SECOND GENERAL MEETING

SUNDAY, MARCH 8 2:00 p.m.—Continental Parlor #5

#### What Is — The Assistant to the Physician? — The Assistant Physician? — The Physician's Assistant? And What Will Be Their Influence on the Practicing Physician?

Moderator: John B. Dillon, M.D., Los Angeles

2:00—The University of Colorado's Training Program for the Pediatric Nurse Practitioner—Henry K. Silver, M.D., Denver, by invitation

2:30—The Pediatric Nurse Practitioner's Experience in Practice—Ethel Gozzi, R.N., King City, by invitation

3:00—The Training Program for the Assistant to the Physician at Duke University—Eugene A. Stead, Jr., M.D., Durham, by invitation

3:30—Questions and Answers Session and Reactor Panel

Members of the Reactor Panel:

The Registered Nurse: Elizabeth Haglund, R.N., San Francisco, by invitation

The Practicing Physician: Glenn E. Austin, M.D., Los Altos

The Medical Student: William Gillanders, San Francisco, by invitation

The Educator: Ruth Sumner, Ph.D., San Francisco, by invitation

The Lawyer: David E. Willett, Esq., San Francisco, by invitation

### THIRD GENERAL MEETING

MONDAY, MARCH 9 1:30 p.m.—Continental Parlor #5

#### Systems of Delivery of Medical Care

Moderator: Ralph W. Burnett, M.D., Bakersfield

1:30—The Impact of Compulsory National Health Insurance on Delivery of Health Care—Mike Gorman, Washington, D.C., by invitation

2:00—The Role of the Medical School in the Development of Prepaid Medical Delivery Systems—Jerome Pollack, B.S., Boston, by invitation

2:30—Private Medical Care Delivery Systems in a Rural Community—L. H. Andrus, M.D., King City

2:50—Community Health Centers and Their Impact on the Delivery of Medical Care—Count D. Gibson, Jr., M.D., Stanford, by invitation

3:10—Bay View-Hunter's Point Referral Center: Its Impact on Medical Care Delivery—Arthur H. Coleman, M.D., San Francisco

3:30—Panel Discussion—Questions and Answers Session



# SECTION MEETINGS

## ALLERGY

*Chairman* . . . . . BAILEY J. LOVIN, JR., M.D., Reseda  
*Secretary* . . . . . E. JAMES YOUNG, M.D., San Mateo  
*Assistant Secretary* . . . . . MILTON MILLMAN, M.D., San Diego

**SUNDAY, MARCH 8** . . . . . 9:00 a.m.—Colonial Room  
 St. Francis Hotel, Union Square

### New Modalities in Treatment of Allergic Disease

9:00—Hetrazan—Max Benis, M.D., Los Angeles  
 9:15—The Treatment of Asthma in Childhood with Cromolyn Sodium—Lawrence Strick, M.D., and Marshall G. Goldberg, M.D., both Encino  
 9:30—Ultrasonic Vaporizer and Other Modalities of Water Vapor Therapy—Daniel H. Wiseman, M.D., Van Nuys, by invitation, and Max Benis, M.D., Los Angeles  
 9:45—Panel Discussion  
 10:00—Recess  
 10:20—Cough: A Common But Often Perplexing Office Problem

### PANEL DISCUSSION— QUESTIONS AND ANSWERS SESSION

Moderator: John S. O'Toole, M.D., Riverside

Members of the Panel: Max K. Pierce, M.D., Los Angeles (Otorhinolaryngology); Birt Harvey, M.D., San Mateo (Pediatrics), by invitation; Ralph Bookman, M.D., Beverly Hills (Allergy); and Charles T. Carman, M.D., San Francisco (Chest Disease).

11:50—Recess  
 12:00—Luncheon and Business Meeting with the California Society of Allergy

**SUNDAY, MARCH 8** . . . . . 2:00 p.m.—Colonel Room  
 St. Francis Hotel, Union Square

### Pathophysiology of Bronchial Asthma

### PANEL DISCUSSION— QUESTIONS AND ANSWERS SESSION

Moderator: Harold S. Novey, M.D., Whittier

2:00—1. Pulmonary Function Tests — Daniel H. Simmons, M.D., Ph.D., Los Angeles, by invitation.  
 2. Regional V/Q Distribution—Archie F. Wilson, M.D., Los Angeles, by invitation  
 3. Is I.P.P.B. Necessary?—Steven E. Levy, M.D., Sherman Oaks, by invitation  
 3:30—Recess

3:50—The Skin Window as a Laboratory Aid in the Diagnosis of Milk Allergy—Joseph D. Bullock, M.D., San Francisco, by invitation

4:05—The Effect of Antihistamines on the Allergic Skin Test—Stanley Galant, M.D., San Francisco, by invitation

4:20—The Use of Cromolyn Sodium in the Treatment of Asthma—James R. Crisp III, M.D., San Francisco, by invitation

4:35—Panel Discussion

5:30—Cocktail Party sponsored by the California Society of Allergy, for members and their guests

## ANESTHESIOLOGY

*Chairman* . . . . . HAMILTON S. DAVIS, M.D., Davis  
*Secretary* . . . . . EDWARD B. SCOTT, M.D., Los Angeles  
*Assistant Secretary* . . . . . PAUL E. THOMAS, M.D., San Diego

**SUNDAY, MARCH 8** . . . . . 9:00 a.m.—Walnut Parlor A  
 Teakwood Parlors A and B

9:00—Coordination of Meeting — Introductory remarks and room assignments, as necessary. Informal round table discussions are scheduled, with from 6 to 8 participants, and chairmen. Cards will list topics for each table, and chairmen, who will be chosen on the basis of their especial interest and familiarity with the assigned topics, will be announced. Discussion periods will be one hour each.

9:15—Round Table Discussions—To be held in rooms assigned at 9:00 a.m.

10:15—Recess—*coffee will be served*

10:45—Round Table Discussions—To be held in rooms assigned at 9:00 a.m.

**SUNDAY, MARCH 8** . . . . . 1:30 p.m.—Walnut Suite

### 1:30— Halothane and Liver Damage

### PANEL DISCUSSION

Moderator: Judson S. Denson, M.D., Los Angeles

Members of the Panel: Joseph J. Buckley, M.D., Minneapolis, by invitation; John P. Bunker, M.D., Palo Alto; William K. Hamilton, M.D., San Francisco; and Telfer B. Reynolds, M.D., Los Angeles.

3:00—Business Meeting

## DERMATOLOGY

Chairman..... CHARLES G. STEFFEN, M.D., Covina  
Secretary..... HAROLD M. SCHNEIDMAN, M.D., San Francisco  
Assistant Secretary..... ROBERT I. FREEDMAN, M.D., Downey

SATURDAY, MARCH 7 10:30 a.m.—San Francisco Medical  
Center, Third and Parnassus Avenues,  
San Francisco

### Pre-Convention Meeting

Robert J. Gorlin, D.D.S., M.S., Minneapolis, by invitation,  
will present a lecture at 10:30 a.m. at the San  
Francisco Medical Center. Auditorium will be posted  
in the lobby.

There will be a clinical meeting of the San Francisco  
Dermatology Society at 1:00 p.m., also at the San  
Francisco Medical Center. Demonstration of patients  
will begin promptly at 1:00 p.m. in the dermatology  
clinic on the third floor, to be followed by a clinical  
discussion of the cases.

Lunch will be available. Parking facilities across from  
the Medical Center.

SUNDAY, MARCH 8 8:30 a.m.—Continental Parlor #2

Program will emphasize

- Congenital Deformities with Associated Skin  
Manifestations
- Skin Problems in the Newborn
- Skin Problems During the First Year of Life

Chairman: Harold M. Schneidman, M.D., San Francisco

8:30—Some Interesting Dermatological Syndromes—Robert J.  
Gorlin, D.D.S., M.S., Minneapolis, by invitation

9:30—Genetic Counseling for Hereditary and Chromosomal  
Disorders—Charles J. Epstein, M.D., San Francisco, by  
invitation

10:30—Neonatal Skin: Its Variations from Adult Skin—Joan E.  
Hodgman, M.D., Los Angeles

Dermatological Problems Peculiar to the Neonatal Pe-  
riod—Robert I. Freedman, M.D., Los Angeles

11:30—Dermatological Problems Peculiar to the First Year of  
Life—Alvin H. Jacobs, M.D., Stanford

12:30—Business Meeting

## GENERAL PRACTICE

Chairman..... ROBERT F. GOBAR, M.D., Daly City  
Secretary..... CLARENCE W. BURRILL, JR., M.D., Westminster  
Assistant Secretary..... LESTER C. KROTCHER, M.D., San Francisco

SUNDAY, MARCH 8 9:00 a.m.—Continental Parlor #5

Combined Meeting with the Section on Pediatrics

Co-sponsored by the American Academy of Pediatrics,  
Chapter I, and the East Bay and Sacramento Pediatric Societies

9:00— Progress in Pediatrics:  
What's New in Newborn Care?

PANEL DISCUSSION

Moderator: William A. Silverman, M.D., San Francisco,  
by invitation

Members of the Panel: Heinz F. Eichenwald, M.D., Dallas; Wil-  
liam Oh, M.D., Torrance; and William H. Tooley,  
M.D., San Francisco, all by invitation

This panel program is arranged for audience participation  
and will cover all the new approaches to neonatal care.  
Each speaker will discuss a facet of the subject and the  
meeting will then be devoted to questions and discussion  
from the audience. Microphones will be available.

TUESDAY, MARCH 10 9:00 a.m.—Continental Parlor #4

### Management of Drug Abuse Problems

9:00—New Directions in Treating Narcotic Addicts—Harold  
T. Conrad, M.D., Lexington, by invitation

9:30—Synanon Methods and Approach—Karl J. Deissler,  
M.D., Oakland

10:00—Methadone Maintenance Techniques—John C. Kramer,  
M.D., Irvine, by invitation

10:30—Drugs of Youth—J. Thomas Ungerleider, M.D., Los  
Angeles

11:00—Panel Discussion—Questions and Answers Session  
Moderator: Robert F. Gobar, Daly City

12:00—Business Meeting

TUESDAY, MARCH 10 2:00 p.m.—Continental Parlor #4

### Recognition and Management of Stresses on the Modern Family

2:00—Early Recognition of Family Disorganization—Lynn P.  
Carmichael, M.D., Miami, by invitation

2:40—Adolescence and Necessary Changes in Family Com-  
munications—Robert H. Oyler, Ph.D., Claremont, by  
invitation

3:20—Sex in Marriage—Walter Ornstein, M.D., La Jolla

4:00—Panel Discussion—Questions and Answers Session  
Moderator: Clarence W. Burrill, Jr., M.D., Westminster

TUESDAY, MARCH 10 12:30 p.m.—1:30 p.m.  
—Garden Room

### Motion Picture Symposium on Drug Abuse

See Motion Picture Program

## GENERAL SURGERY

Chairman..... HAROLD H. LINDNER, M.D., San Francisco  
Secretary..... JAMES W. MARTIN, M.D., Sacramento  
Assistant Secretary..... MARSHALL J. ORLOFF, M.D., San Diego

TUESDAY, MARCH 10 9:00 a.m.—Continental Parlor  
#2 and #3

Program to be announced

TUESDAY, MARCH 10 2:00 p.m.—Continental Parlor  
#2 and #3

Program to be announced

INDUSTRIAL MEDICINE AND SURGERY

Chairman.....DAVID P. DISCHER, M.D., Northridge  
Secretary.....WALTER J. GILLOGLEY, M.D., Sunnyvale  
Assistant Secretary.CHARLES E. SCHOETTIN, M.D., Los Angeles

SATURDAY, MARCH 7 9:00 a.m.—Hilton Plaza

Joint Meeting with the Section on Orthopedics

The Comprehensive Treatment of the Industrially Injured

9:00—The program will present a comprehensive examination of medical procedures, laws, fees and road-blocks in the treatment and rehabilitation of the disabled employee. Participants will include prominent physicians, insurance company executives, the Chairman of the Workmen's Compensation Appeals Board, State legislators in the workmen's compensation field, and medical directors of nationally organized companies.

Program and speakers to be announced.

12:30—Luncheon with the Section on Orthopedics  
Luncheon Address: To be announced  
Advance reservations are necessary

INTERNAL MEDICINE

Chairman.....PETTUS G. SECREST, M.D., San Francisco  
Secretary.....GLENN MOLYNEAUX, M.D., San Francisco  
Assistant Secretary.....WILLIAM M. TODD, M.D., Long Beach

All Sessions

Presented Jointly by the Section on Internal Medicine and the Departments of Medicine, University of California, Davis, School of Medicine; University of California, San Francisco Medical Center; and Stanford University School of Medicine

SATURDAY, MARCH 7 9:00 a.m.—Whitney Room  
Shasta Room, Tamalpais Room

Consult the Experts

These are simultaneous and informal round table discussions, in which audience participation is anticipated. The groups will recess at 9:50 a.m. and 10:50 a.m., at which times the discussion leaders will move to a different room and continue with the same topic.

9:00—WHITNEY ROOM

Malabsorption States

Robert J. Bolt, M.D., Davis, and Marvin H. Sleisenger, M.D., San Francisco, both by invitation

9:00—SHASTA ROOM

Treatment of Difficult Diabetics

Peter H. Forsham, M.D., San Francisco, and Gerald M. Reaven, M.D., Stanford, by invitation

9:00—TAMALPAIS ROOM

Pulmonary Insufficiency

John F. Murray, M.D., San Francisco, and Carroll E. Cross, M.D., Davis

SUNDAY, MARCH 8 9:00 a.m.—Whitney Room  
Shasta Room, Tamalpais Room

Consult the Experts

These are simultaneous and informal round table discussions, in which audience participation is anticipated. The groups will recess at 9:50 a.m. and 10:50 a.m., at which times the discussion leaders will move to a different room and continue with the same topic.

9:00—WHITNEY ROOM

New Syndromes of Rheumatic Disease

Halsted R. Holman, M.D., and Hugh O. McDevitt, M.D., both Stanford, by invitation

9:00—SHASTA ROOM

Arrhythmias

James F. Spann, Jr., M.D., and Ezra A. Amsterdam, M.D., both Davis, by invitation

9:00—TAMALPAIS ROOM

Drug Abuse

David E. Smith, M.D., San Francisco, and Leo E. Hollister, M.D., Stanford, by invitation

MONDAY, MARCH 9 9:00 a.m.—Whitney Room  
Shasta Room, Tamalpais Room

Consult the Experts

These are simultaneous and informal round table discussions, in which audience participation is anticipated. The groups will recess at 9:50 a.m. and 10:50 a.m., at which times the discussion leaders will move to a different room and continue with the same topic.

9:00—WHITNEY ROOM

Kidney Stones—Pathogenesis and Treatment

Lloyd H. Smith, Jr., M.D., by invitation, and Felix O. Kolb, M.D., both San Francisco

9:00—SHASTA ROOM

Hyperlipidemias

Richard J. Havel, M.D., San Francisco, and Robert F. Zelis, M.D., Davis, both by invitation

9:00—TAMALPAIS ROOM

Coma — Differential Diagnosis

David A. Prince, M.D., and Gary M. Gray, M.D., both Stanford, by invitation

11:50—Recess

12:00—Business Meeting



## OBSTETRICS AND GYNECOLOGY

*Chairman* . . . . . CLIFFORD C. CHAPPELL, M.D., Berkeley  
*Secretary* . . . . . JAMES C. CAILLOUETTE, M.D., Pasadena  
*Assistant Secretary* . . . . . JESSE A. RUST, JR., M.D., San Diego

MONDAY, MARCH 9 . . . . . 8:30 a.m.—Hilton Plaza

Chairman: James C. Caillouette, M.D., Pasadena

8:30—Office Urethroscopy—Jack R. Robertson, M.D., Santa Maria

9:00—Induction of Ovulation: Observations on the Use of Clomid, Pergonal, and Human Gonadotropin—Robert W. Kistner, M.D., Boston, by invitation

10:00—Recess

10:15—The Good and the Bad of Therapeutic Abortions—Paul H. Brenner, M.D., Solana Beach

10:45—Estril in the Management of Diabetic Pregnancies—Gail V. Anderson, M.D., Los Angeles

11:15—Anesthetic Drug Levels in Fetal Blood During Labor and Delivery Following Regional Anesthesia—Robert O. Bauer, M.D., Los Angeles

12:00—Joint Luncheon with the California Division of the American College of Obstetricians and Gynecologists

Luncheon Address: Clinical Application of Synthetic Progestins—Robert W. Kistner, M.D., Boston, by invitation

Advance reservations may be made by contacting William K. Graves, M.D., 490 Post Street, San Francisco 94102, (415) 986-2213.

MONDAY, MARCH 9 . . . . . 2:00 p.m.—Hilton Plaza

2:00—Problems in the Use of Contraceptives

PANEL DISCUSSION

Moderator: Edmund W. Overstreet, M.D., San Francisco

2:00—Case Presentation—Clifford C. Chappell, M.D., Berkeley

Introduction of Panel—Clifford C. Chappell, M.D., Berkeley

Members of the Panel: To be announced

3:30—Recess

3:35—Business Meeting

## OPHTHALMOLOGY

*Chairman* . . . . . J. P. McBRIDE, M.D., Los Angeles  
*Secretary* . . . . . THEODORE STEINBERG, M.D., Fresno  
*Assistant Secretary* . . . . . GEORGE K. KAMBARA, M.D., Los Angeles

SUNDAY, MARCH 8 . . . . . 2:00 p.m.—Teakwood Suite

Chairman: J. P. McBride, M.D., Los Angeles

2:00—The Surgical Treatment of Retinal Detachments without Drainage of Subretinal Fluid—M. Wallace Friedman, M.D., San Francisco

2:30—The Force Generation Test in Paralytic Strabismus—Alan B. Scott, M.D., San Francisco

3:00—Fluorescein Angiography of the Optic Nerve in Glaucoma—John Hetherington, Jr., M.D., San Francisco

3:30—Photocoagulation Treatment of Senile Macular Degeneration (report of series)—Wayne E. Fung, M.D., San Francisco

4:00—Business Meeting

## ORTHOPEDICS

*Chairman* . . . . . JOHN A. BLOSSER, M.D., Oakland  
*Secretary* . . . . . CHADWICK F. SMITH, M.D., Los Angeles  
*Assistant Secretary* . . . . . HAROLD H. ROBINSON, M.D., Sacramento

SATURDAY, MARCH 7 . . . . . 9:00 a.m.—Hilton Plaza

*Joint Meeting with the Section on Industrial Medicine and Surgery*

### The Comprehensive Treatment of the Industrially Injured

9:00—The program will present a comprehensive examination of medical procedures, laws, fees and roadblocks in the treatment and rehabilitation of the disabled employee. Participants will include prominent physicians, insurance company executives, the Chairman of the Workmen's Compensation Appeals Board, State legislators in the workmen's compensation field, and medical directors of nationally organized companies.

Program and speakers to be announced.

12:30—Luncheon with the Section on Industrial Medicine and Surgery

Luncheon Address: To be announced

Advance reservations are necessary

## OTOLARYNGOLOGY

*Chairman*.....EMILE COUGH, M.D., Stockton  
*Secretary*.....EDWARD A. KANTOR, M.D., Beverly Hills  
*Assistant Secretary*.....HERBERT DEDO, M.D., San Francisco

**SUNDAY, MARCH 8**                      9:30 a.m.—Walnut Parlor B

- 9:30—1. Rare and Interesting Lesions of the Parotid Gland—  
Alfred D. Katz, M.D., Los Angeles
2. Tracheal Fenestration in Chronic Lung Disease—  
Leon W. Lipson, M.D., Stanford, by invitation
3. Surgical Treatment of Malignant Exophthalmos —  
Robert Maltz, M.D., Stanford, by invitation
4. Rehabilitation of Speech and Swallowing Function  
Following Cancer Surgery — Richard L. Goode,  
M.D., Stanford
5. Advances in Esophagoscopy: The Fiber Optic  
Esophagoscope—Frank J. Novak, M.D., and Richard  
L. Goode, M.D., both Stanford
6. Office Cryosurgical Treatment of Oral Leuko-  
plakia—Richard L. Goode, M.D., Stanford

12:30—Business Meeting

## --- PATHOLOGY

*Chairman*.....JEROME L. HEARD, M.D., San Diego  
*Secretary*.....OSMAN H. HULL, M.D., Monterey  
*Assistant Secretary*.....ROBERT S. COX, JR., M.D., San Jose

**SATURDAY, MARCH 7**                      9:00 a.m.—Walnut Suite

### Multiphasic Screening

- 9:00—Introductory Remarks—Robert S. Cox, Jr., M.D., San  
Jose
- 9:10—Multiphasic Screening: Some On-Line Perspectives—  
John H. Yoell, M.D., Los Angeles
- 9:30—Economics and Logistics of Mass Multiphasic Screening  
—Michael S. Muldavin, M.S.(Ec.), M.P.H., LL.B.,  
Berkeley, by invitation
- 9:50—Multiphasic Screening in the Clinic Setting—Joseph La-  
Dou, M.D., Palo Alto, by invitation
- 10:10—Recess
- 10:30—The Objectives and Future of Laboratory Medicine—  
Jon V. Straumfjord, Jr., M.D., Ph.D., Birmingham, Ala.,  
by invitation

11:15—Influence of Age and Sex on Normal Values of Serum  
Chemistry—R. Eugene Tolls, M.D., San Francisco, and  
Mario Werner, M.D., St. Louis, by invitation

11:45—Panel Discussion

12:30—Luncheon with the AMA-Approved Schools of Medical  
Technology

**SATURDAY, MARCH 7**                      2:00 p.m.—Continental Parlor #1

2:00—Business Meeting—Section on Pathology

2:15—Business Meeting—California Society of Pathologists

**SUNDAY, MARCH 8**                      9:00 a.m. to 5:30 p.m.  
—Continental Parlor #4

## PATHOLOGY CONFERENCE

*Committee on Cancer, California Medical Association*

### Tumors of the Thyroid

Moderator: J. Beach Hazard, M.D., Cleveland, by invitation

9:00 a.m. to 12:30 p.m.—2:00 p.m. to 5:30 p.m.

The registration fee for this Conference is \$30.00,  
which includes attendance, a set of 25 slides, protocol  
and addenda. For attendance only, the fee is \$15.00.  
There is no charge for residents and interns. Those  
wishing to attend are requested to register with Wel-  
don K. Bullock, M.D., Executive Director, Tumor  
Tissue Registry, CMA Committee on Cancer, Los An-  
geles County-University of Southern California Medi-  
cal Center, 1200 North State Street, Los Angeles 90033.

**MONDAY, MARCH 9**                      9:30 a.m.—Teakwood Suite

*Co-Sponsored with the Section on Urology*

### Progress in Cytologic and Chemical Diagnosis of Genitourinary Diseases

- 9:30—Genitourinary Cytology—Eileen B. King, M.D., San  
Francisco
- 10:00—The Dependability of Chemical and Cytologic Tests in  
Genitourinary Disease—William H. Kern, M.D., Los  
Angeles
- 10:30—Recess
- 10:45—Application of New Chemical Diagnostic Tests—R. F.  
Gittes, M.D., San Diego, by invitation
- 11:15—Application of New Cytologic Diagnostic Tests—Mat-  
lock M. Mims, M.D., Los Angeles

## PEDIATRICS

Chairman.....EUGENE GETTELMAN, M.D., Encino  
Secretary.....CHESTER TANCREDI, M.D., San Diego  
Assistant Secretary...WILLIAM M. JENKINS, JR., M.D., Oakland

SUNDAY, MARCH 8 9:00 a.m.—Continental Parlor #5

*Combined Meeting with the Section on General Practice  
Co-Sponsored by the American Academy of Pediatrics,  
Chapter I, and the East Bay and Sacramento Pediatric Societies*

9:00— **Progress in Pediatrics:  
What's New in Newborn Care?**

PANEL DISCUSSION

Moderator: William A. Silverman, M.D., San Francisco,  
by invitation

Members of the Panel: Heinz F. Eichenwald, M.D., Dallas; William Oh, M.D., Torrance; and William H. Tooley, M.D., San Francisco, all by invitation.

This panel program is arranged for audience participation and will cover all the new approaches to neonatal care. Each speaker will discuss a facet of the subject and the meeting will then be devoted to questions and discussion from the audience. Microphones will be available.

MONDAY, MARCH 9 9:00 a.m.-12 noon—Garden Room

### Motion Picture Symposium on Pediatrics

See Motion Picture Program

MONDAY, MARCH 9 12:00 noon—Continental Parlor #4

12:00—Luncheon with the American Academy of Pediatrics,  
Chapter I

Luncheon Address: Child Health: Who Cares?—Philip R. Lee, M.D., San Francisco

Advance reservations may be made by contacting Alexander Hatoff, M.D., Highland General Hospital, 2701 14th Avenue, Oakland 94606, (415) 534-8055.

MONDAY, MARCH 9 1:30 p.m.—Continental Parlor #4

Chairman: Eugene Gettelman, M.D., Encino

1:30—A Review of Antimicrobial Therapy As It Is In 1970—Heinz F. Eichenwald, M.D., Dallas, by invitation

2:30—Upper Respiratory Problems in Children

PANEL DISCUSSION

1. What to do about the Child with a Running Nose and Frequent Colds—Van Vleck Chambers, M.D., Palo Alto
2. The Otolaryngologist's Viewpoint—Henry J. Rubin, M.D., Beverly Hills
3. Virus Infections—Moses Grossman, M.D., San Francisco
4. Antibiotics: Use or Abuse—Heinz F. Eichenwald, M.D., Dallas, by invitation

4:30—Business Meeting

## PHYSICAL MEDICINE AND REHABILITATION

Chairman.....S. MALVERN DORINSON, M.D., San Francisco  
Secretary.....ROBERT V. MILLER, JR., M.D., Encino  
Assistant Secretary.....JOSEPH N. VIZZARD, M.D., Los Gatos

SUNDAY, MARCH 8 1:30 p.m.—Continental Parlor #2

### Sexual Myths and Concepts in Physical Disabilities

- 1:30—1. The Sexual Myth—Robert G. Milligan, Ph.D., San Francisco, by invitation
2. Sexual Concepts in Traumatic Cord Lesions—A. Estin Comarr, M.D., Long Beach, by invitation
3. Sexual Concepts in Cervicospinal and Lumbosacral Injuries—David Rubin, M.D., Los Angeles
4. Sexual Concepts in Acquired Upper and Lower Motoneuron Disease—Speaker to be announced
5. Coping with Impotents—Carroll M. Brodsky, M.D., San Francisco

4:00—Business Meeting

## PLASTIC SURGERY

Acting Chairman.....FRANKLIN L. ASHLEY, M.D., Los Angeles

SUNDAY, MARCH 8 9:00 a.m.—Continental Parlor #1

Program to be announced

SUNDAY, MARCH 8 1:30 p.m.—Continental Parlor #1

Program to be announced

## PREVENTIVE MEDICINE AND PUBLIC HEALTH

Chairman.....ALLEN C. NEISWANDER, M.D., Whittier  
Secretary.....GLEN W. KENT, M.D., Martinez  
Assistant Secretary.....STEPHEN A. CORAY, M.D., Oakview

MONDAY, MARCH 9 2:00 p.m.—Walnut Suite

### Pressures: Population, Political and Planning — or Are We Going For Broke?

- 2:00—Population Pressures—Philip R. Lee, M.D., San Francisco
- 2:20—Political Pressures—Louis F. Saylor, M.D., Berkeley
- 2:50—Planning Pressures—Henrik L. Blum, M.D., Berkeley
- 3:10—Recess
- 3:20—Prevention of Illness Due to Poverty, Overcrowding and Ignorance: A New Approach—Louis S. Baer, M.D., Burlingame
- 3:40—Questions and Answers Session
- 4:00—Business Meeting



PSYCHIATRY AND NEUROLOGY

Chairman . . . . . HERBERT VANDERVOORT, M.D., San Francisco  
Secretary . . . . . SYDNEY L. POMER, M.D., Los Angeles  
Assistant Secretary . MORTON K. RUBINSTEIN, M.D., Los Angeles

SATURDAY, MARCH 7 9:30 a.m.—Teakwood Suite

- 9:30—Encephalopathies of Unusual Etiology — Pierre M. Dreyfus, M.D., Davis, by invitation
- 10:00—Diabetic Neuropathies—Arthur K. Asbury, M.D., San Francisco, by invitation
- 10:30—L-Dopa in the Management of Parkinsonism—William W. Hofmann, M.D., Palo Alto, by invitation
- 11:00—Alcoholic Neurologic Disorders—Neil H. Raskin, M.D., San Francisco, by invitation

11:30—  
PANEL DISCUSSION  
Moderator: Morton K. Rubinstein, M.D., Los Angeles  
Members of the Panel: Arthur K. Asbury, M.D., San Francisco; Pierre M. Dreyfus, M.D., Davis; William W. Hofmann, M.D., Palo Alto; and Neil H. Raskin, M.D., San Francisco, all by invitation.

12:00—Business Meeting

SATURDAY, MARCH 7 2:00 p.m.—Continental Parlor #3

- 2:00—The Place of Electro-Sleep in Psychiatry and Medicine —Ronald R. Koegler, M.D., Los Angeles; Shelby M. Hicks, M.D., Merced; and James H. Barger, M.D., Olive View, by invitation
  - 2:30—Frontal Lobotomy in Early Schizophrenia: A Long-Range Follow-Up of 350 Cases—Walter J. Freeman, M.D., Berkeley, by invitation
  - 3:00—  
PANEL DISCUSSION  
Moderator: Sydney L. Pomer, M.D., Los Angeles
  - 3:00—Homosexuality: A Medical Problem of Social Proportions—Charles W. Socarides, M.D., New York City, by invitation
- Members of the Panel: Bernard L. Diamond, M.D., Berkeley, and Norman Reider, M.D., San Francisco.

RADIOLOGY

Chairman . . . . . H. JOACHIM BURHENNE, M.D., San Francisco  
Secretary . . . . . MATHEW E. O'KEEFE, JR., M.D., Whittier  
Assistant Secretary . . WARREN M. RUSSELL, M.D., San Francisco

SATURDAY, MARCH 7 9:30 a.m. to 5:00 p.m.  
—Italian Room  
St. Francis Hotel, Union Square

Radiology Conference

Committee on Cancer, California Medical Association  
Chairman: Gerald M. McDonnel, M.D., Los Angeles  
Secretary: Robert H. Reid, M.D., Los Gatos

- 9:30 a.m. to 12:00 noon—THERAPY SESSION
- 1:30 p.m. to 3:30 p.m.—DIAGNOSTIC SESSION

SUNDAY, MARCH 8 9:30 a.m.—Italian Room  
St. Francis Hotel, Union Square

- 9:30—Radionucleide Studies of Ventricular Perfusion—William L. Ashburn, M.D., San Diego, by invitation
- 9:45—Kidney Visualization with Radioisotopes in the Azotemic Patient—Leslie R. Bennett, M.D., Los Angeles
- 10:00—Experience with Mammography, Thermography and Xeromammography in the Detection of Breast Cancer —Andrew H. Dowdy, M.D., Los Angeles
- 10:15—Perinatal Pulmonary Roentgenography — William H. Northway, Jr., M.D., Palo Alto, by invitation
- 10:30—Radiologic Intra-Arterial Treatment of Gastrointestinal Bleeding—Josef Rösch, M.D., Prague, Czechoslovakia, by invitation
- 10:45—Muco-Polysaccharidosis—Jack Edeiken, M.D., Philadelphia, by invitation
- 11:00—The Impacted Wisdom Tooth — William Campbell, M.D., D.M.R.D., East Grinstead, Sussex, England, by invitation
- 11:15—Spinal and Pelvic Changes Following Labor—W. Peter Cockshott, M.D., Hamilton, Ontario, Canada, by invitation
- 11:30—Mechanical Complications of Myocardial Infarction—M. J. Raphael, M.B., London, England, by invitation
- 11:45—Vascular Disease of the Small Bowel and Colon—Richard H. Marshak, M.D., New York City, by invitation
- 12:00—Business Meeting

SUNDAY, MARCH 8 2:00 p.m.—Italian Room  
St. Francis Hotel, Union Square

Fourth Annual  
L. Henry Garland Memorial Lecture

Sponsored by the California Radiological Society

- 2:00—Introduction—Reynold F. Brown, M.D., San Francisco, President, California Radiological Society
- 2:05—A Breakthrough in the Battle with Coronary Artery Obstructive Disease—Melvin P. Judkins, M.D., Portland, by invitation
- 3:00—Recess
- 3:15—Annual Meeting—California Radiological Society

## UROLOGY

Chairman . . . . . MILTON ROSENBERG, M.D., San Francisco  
Secretary . . . . . ROBERT A. C. BRIDGE, M.D., San Diego  
Assistant Secretary . . . . . JAY R. LONGLEY, M.D., Newport Beach

MONDAY, MARCH 9 . . . . . 9:30 a.m.—Teakwood Suite  
*Co-Sponsored with the Section on Pathology*

### Progress in Cytologic and Chemical Diagnosis of Genitourinary Diseases

9:30—Genitourinary Cytology—Eileen B. King, M.D., San Francisco  
10:00—The Dependability of Chemical and Cytologic Tests in Genitourinary Disease—William H. Kern, M.D., Los Angeles  
10:30—Recess  
10:45—Application of New Chemical Diagnostic Tests—R. F. Gittes, M.D., San Diego, by invitation

11:15—Application of New Cytologic Diagnostic Tests—Matlock M. Mims, M.D., Los Angeles

## MONDAY, MARCH 9

2:00 p.m.—Teakwood Suite

2:00—Carcinoma of the Prostate—Frank J. Leary, M.D., Rochester, Minn., by invitation  
2:30—Vasovasostomies: Techniques and Results—Julius H. Winer, M.D., Beverly Hills  
2:45—  
*Discussant*—Jay R. Longley, M.D., Newport Beach  
3:00—Autotransfusion in Transurethral Prostatic Resection—Frank J. Leary, M.D., Rochester, Minn., by invitation  
3:30—Business Meeting  
4:00—Socio-Economic Aspects of Urology in the California Medical Association—James L. Goebel, M.D., Ross; Harold Kay, M.D., Oakland; and Sam Peck, M.D., San Diego

# MOTION PICTURE PROGRAM

## Garden Room      Hilton Hotel

### Co-Chairmen

Richard E. Gardner, M.D., San Francisco

W. Morris H. Noble, M.D., San Francisco

Five film symposia will be presented, each utilizing about two-thirds of the time for projecting of films, and one-third for discussion, questions and answers.

### SUNDAY, MARCH 8

2:00 p.m.

2:00—

#### SURGERY

Moderator: John M. Erskine, M.D., San Francisco

Discussants to be announced

2:00—Introduction.

1. Reversed Jejunal Segment for Disabling Post-Vagotomy Diarrhea — J. Lynwood Herrington, Jr., M.D., and John L. Sawyers, M.D., both Nashville.
2. Treatment of Abdominal Trauma — J. Bradley Aust, M.D., and H. David Root, M.D., both San Antonio.
3. Prevention of Pulmonary Embolism: A New Catheter Technique for Interruption of Inferior Vena Cava — James R. Jude, M.D., and Kazi Mobin-Uddin, M.D., both Miami.
4. Surgical Treatment of Benign Breast Diseases —David V. Habif, M.D., and George A. Knaysi, M.D., both New York.

### MONDAY, MARCH 9

9:00 a.m.

9:00—

#### PEDIATRICS

*Sponsored by Section on Pediatrics*

Moderator: Eugene Gettelman, M.D., Encino

9:00—Introduction.

Partial listing of films.

1. Oral Lesions in Children and Adults — Paul V. Woolley, Jr., M.D., Howard P. Lewis, M.D., James Avery, D.D.S., Carl Witkop, D.D.S., and Fred A. Henney, D.D.S., all Michigan.

Discussant: Richard Leonards, M.D., San Francisco.

2. Second Chance — J. L. Schulman, M.D., Chicago.

Discussant: Robert G. Patton, M.D., San Francisco.

### MONDAY, MARCH 9

2:00 p.m.

2:00—

#### PRACTICAL PROBLEMS IN SURGERY

Moderator: Richard E. Gardner, M.D., San Francisco.

Discussants to be announced.

2:00—Introduction.

1. Varicose Veins — Wiley F. Barker, M.D., Los Angeles.
2. Femoral Hernioplasty — Chester B. McVay, M.D., Yankton, South Dakota.
3. Lord Procedure for Repair of Hydrocele — George J. Bulkley, M.D., Chicago; and George W. Kaplan, M.D., San Diego.
4. Snake Bite! — Larry D. Ruth, M.D., Clifford C. Snyder, M.D., and Gary R. Hunter, all Salt Lake City.

### TUESDAY, MARCH 10

9:00 a.m.

9:00—

#### MEDICINE

Moderator: W. Morris H. Noble, M.D., San Francisco

9:00—Introduction.

Partial listing of films.

1. The Technique of Intra-Articular and Peri-Articular Injection — Edward W. Boland, M.D., Los Angeles.

Discussant: Ronald L. Kaye, M.D., Palo Alto.

2. Aldosterone—Story of a Hormone—Edward G. Biglieri, M.D., San Francisco; Patrick J. Mulrow, M.D., Orange, Conn.; and Louis J. Tobian, M.D., Minneapolis.

### TUESDAY, MARCH 10

12:30 p.m.

12:30—

#### DRUG ABUSE

*Sponsored by Section on General Practice*

Moderator: Clarence W. Burrill, Jr., M.D., Westminster

Film to be announced



# SCIENTIFIC AND ORGANIZATIONAL EXHIBITS

## California Room

**European Innovations in Emergency Health Care Services** — Robert Earl Burky, M.D., San Francisco, by invitation. This exhibit shows emergency care services in Belgium, Germany, Denmark, and Sweden and compares them to those in the United States. Details of emergency health communications, ambulance services, training of ambulance attendants, and miscellaneous equipment for emergency care are given.

**California Society of Plastic and Reconstructive Surgeons** — Raymond R. Kauffman, M.D., Burlingame. This exhibit is prepared to coincide with the creation of the 19th Scientific Section of the California Medical Association, the section on Plastic Surgery. The exhibit presents a cross section of cases representing an approach to treatment of (1) trauma, including burns, (2) congenital deformities (e.g., cleft lip/palate), (3) reconstruction problems following radical surgery for carcinoma, e.g., (a) jaw reconstruction (b) eyelid reconstruction (c) nose reconstruction.

**Man versus Arthropods**—Mrs. Karen Steffensen, Chicago by invitation. The exhibit "Man versus Arthropods" describes reactions produced in the human being by various insects—the bee, spider, and chigger as well as several others. Pictures and drawings of the insects are included, along with descriptions and pictures of the reactions produced. The treatment for each type of reaction is summarized; also mentioned are two methods for desensitizing people who are allergic to the sting of the bee, wasp, or yellow jacket. Such people become sensitized to a particular venom after repeated stinging by the insect, and the victim develops an allergic response that may result in a severe reaction and even death. Protection against arthropods involves mass eradication of insect pests; several methods are listed. For protecting the individual person, repellents that can be applied to the skin are most practical. In addition, the clothing may be impregnated with repellents. Most of those presently available are removed when the clothes are washed.

**Diagnosis and Treatment of Rheumatoid Arthritis** — William R. Murray, M.D., San Francisco. The exhibit describes the diagnosis and treatment of rheumatoid arthritis both surgical and non-surgical. The wrist and knee are used as representative joints. Demonstrations are shown on non-surgical bracing and splinting as well as photographs and x-rays of wrists and knees before, during, and after synovectomy, tendon transposition, arthrodesis, osteotomy and arthroplasty. Basic details of surgical technique are outlined. The exhibit is a self-contained unit.

**Pollution**—Medical Research Association of California. The exhibit consists of photographs of lung tissue sections demonstrating the effects of pollution on lung tissues.

**Birth Defects Prevention**—The National Foundation. The center panel illustrates the services provided in Birth Defects Centers. The text accompanying each illustration explains the services. The two side panels contain illuminated transparencies of a missing thumb, visceral hernia and hydrocephalus, (before and after surgery) and a child with phocomelia (missing limbs) before and with prostheses.

**Clinical Electromyography in the Acute General Hospital** — Elizabeth Austin, M.D., Los Angeles. The exhibit demonstrates basic physiological principles of clinical electromyography, particularly in the detection of radiculopathy and peripheral neuropathy. A live demonstration will be given of motor and sensory nerve conduction velocities and latencies and their clinical application in nerve compression syndromes.

**Some Lessons from Recent Coccidioidal Fatalities** — Robert W. Huntington, M.D., and Owen A. Kearns, M.D., Bakersfield. Brief case legends and microphotographs illustrate situations in which Amphotericin was (a) ineffective or (b) toxic, and of diagnostic failures. The moral need for a safer and more efficacious drug, for greater diagnostic alertness, and for realization that the confirmation of the diagnosis of coccidioidomycosis may constitute a medical emergency.

**Synanon: A Healthy Community** — Karl J. Deissler, M.D., Oakland. Synanon representatives will be on hand to answer questions and distribute literature.

**California Committee on Regional Medical Programs** — Paul D. Ward, San Francisco, by invitation. The exhibit will describe, through photomurals and a minimum of copy block text, key features of the operational activities funded in California under Public Law 89-239. There will also be descriptions of the status of Comprehensive Health Planning in California.

**Medical Aspects in the Social Security Disability Program** — Benjamin Lieberman, M.D., Oakland; Don Kimmerling, M.D., and George Simko, M.D., Oakland, both by invitation. The exhibit describes the principles and regulations underlying disability determinations in this Federal Program; exemplified by cardiac impairments. The California Department of Rehabilitation has processed, since 1956, about 10 percent of the national volume of applications for disability insurance under Social Security, or about 500,000. A brochure, and other material, will be distributed to physicians.

**The Problems of Drug Utilization** — Norman De Nosaquo, M.D., Chicago, by invitation. This exhibit presents problems of drug utilization including adverse reactions and the educational material available on this subject through the A.M.A. Department of Drugs. Reprints and brochures listing reactions in different specialty areas (e.g., allergy, pediatrics, hematology, etc.) will be available.

# OFFICERS AND DELEGATES

## General Officers

Albert G. Miller, San Mateo	President
Ralph W. Burnett, Bakersfield	President-Elect
William F. Quinn, Los Angeles	Speaker, House of Delegates
Joseph F. Boyle, Los Angeles	Vice-Speaker, House of Delegates
Harold Kay, Oakland	Chairman of Council
Helen B. Weyrauch, San Francisco	Secretary
Malcolm S. M. Watts, San Francisco	Editor
Robert L. Thomas	Executive Director
Hassard, Bonnington, Rogers & Huber	Legal Counsel

## House of Delegates

TOTAL DELEGATES (353)

DELEGATES EX-OFFICIO (72)

Albert G. Miller, San Mateo	President
Ralph W. Burnett, Bakersfield	President-Elect
William F. Quinn, Los Angeles	Speaker, House of Delegates
Joseph F. Boyle, Los Angeles	Vice-Speaker, House of Delegates
Harold Kay, Oakland	Chairman of Council
Helen B. Weyrauch, San Francisco	Secretary
Malcolm S. M. Watts, San Francisco	Editor

### COUNCILORS

Stanley A. Moore (1970)	First District
Nicholas P. Krikes (1971)	Second District
Henry V. Eastman (1970)	Third District
M. M. Haskell (1971)	Office No. 1, Fourth District
Elmer F. Gooel (1972)	Office No. 2, Fourth District
Homer C. Pheasant (1970)	Office No. 3, Fourth District
Lewis T. Bullock (1971)	Office No. 4, Fourth District

Joseph P. O'Connor (1972)	Office No. 5, Fourth District
Marvin J. Shapiro (1970)	Office No. 6, Fourth District
George C. Andersen (1971)	Office No. 7, Fourth District
Jean F. Crum (1972)	Office No. 8, Fourth District
Frank A. Rogers (1970)	Office No. 9, Fourth District
Joseph F. Maguire (1970)	Fifth District
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John T. Saidy (1971)	Office No. 2, Seventh District
Albert G. Clark (1972)	Office No. 1, Eighth District
Roberta F. Fenlon (1970)	Office No. 2, Eighth District
Harold Kay (1972)	Office No. 1, Ninth District
Frederick W. Ackerman (1970)	Office No. 2, Ninth District
E. Kash Rose (1970)	Tenth District
Thomas N. Elmendorf (1971)	Eleventh District
Forest J. Grunigen (1970)	Twelfth District
Charles J. Tupper (1970)	Scientific Board Representative

ELECTED DELEGATES (281)

Delegates	Alternates
<b>ALAMEDA-CONTRA COSTA (20)</b>	
Anderson, Bruce M.	Adams, Richard Paul
Anderson, Conrad E.	Adams, Robert
Boysen, Edwin E.	Barber, Thomas E.
Buehler, John M.	Bassett, J. Brandon
Davis, Aaron E.	Cangelo, Vincent W.
Davis, Velma L.	Cherry, Donald W.
Goodman, Julien M.	Cohen, James I.
Greist, Elwood C.	Cook, Wallace H.
Holden, Herbert	Dooley, John D.
Hoskins, H. Dean	Duffy, Charles C.
Hudson, Charles B.	Frost, Gordon
Juul, Clement O.	Goetsch, Carl
Kunkel, Peter	Hartzell, Walter J.
Lewis, Gwilym B.	Kirk, Ralph
Murphy, Joseph P.	Martin, L. Robert
Neighbor, Jean E.	Plaut, Eric A.
Palmer, Rodney I.	Ross, Joseph
Powell, Oscar M.	Shapiro, Robert L.
Purcell, Edward F.	Upton, Albert L.
Richards, Dexter N.	Vickery, John E., Jr.

<b>BUTTE-GLENN (2)</b>	
Murphy, Franklin L.	Hubbard, C. K.
Ritter, Dale W.	Sears, Adrian R. M.

### FORTY-FIRST (2)

### FRESNO (5)

Argo, W. L.	DeFries, William
Millar, Max S.	Ginsburg, H. M.
Smith, Robb	Kass, Robert
Snyder, L. J.	Tostenson, N. E.
Steinberg, Theodore	Wilde, N. John

Delegates	Alternates
<b>HUMBOLDT-DEL NORTE (2)</b>	
<b>IMPERIAL (2)</b>	
<b>INTO-MONO (2)</b>	
<b>KERN (4)</b>	
Day, Robert L.	Anderson, Gene
Osell, L. N.	Clark, M. Marlin
Strongin, Seymour	Reese, Thomas V.
Vaughan, J. E.	Spaulding, Keith W.
<b>KINGS (2)</b>	
Brookshier, R. W.	Barreiro, A. L.
Kerr, Edwin E.	Dean, James E.
<b>LASSEN-PLUMAS-MODOC-SIERRA (2)</b>	
Korver, Kenneth G.	Batson, Wilbur C.
Quinn, William J.	Winchell, Robert J.

### LOS ANGELES (92)

Adams, Donald A.	Affley, Harry J., Jr.
Alter, Marvin S.	Alban, Seymour L.
Andersen, George C.	Alexakis, Peter
Anderson, Richard E.	Allen, Robert F.
Asher, Leonard M.	Amerongen, Frederick K.
Attyah, Albert M.	Bergin, William F.
Austin, R. Reed	Bergreen, Stanley W.
Axelrod, Bernard	Bleifer, Daniel J.
Bailey, Wilbur	Bradley, Gerald H.
Baker, Jack W.	Breitman, Gordon
Beason, Ralph D.	Brennan, James E.
Bernstein, Harold	Bruckner, Sherman H.
Bills, Jack W.	Carney, Padraig
Blood, William	Cobb, Dudley M., Jr.

### Delegates

Bowen, Gordon T.  
Boyle, Joseph F.  
Breakstone, Gerald J.  
Brennan, John C.  
Briney, Allan K.  
Buehler, George S.  
Bullock, Lewis T.  
Cope, Jerome A.  
D'Orazio, Edward  
Dorn, Robert M.  
Doyle, John B., Jr.  
Dukes, Robert W.  
Ellerbeck, Walter P.  
Elshire, H. Donel  
Evashwick, George  
Feldman, David H.  
Fields, Albert  
Fitch, Donald R.  
Ford, James H.  
Fox, James B.  
Frank, William P.  
Freeman, Gordon L.  
Goodwin, William E.  
Halasey, Thomas  
Haschka, August J., Jr.  
Hill, Harry E.  
Hormer, David B.  
Horowitz, Samuel  
Jones, Henry A.  
Ketcham, Burton E., Jr.  
Kiddie, Thomas  
Kugel, Arthur I.  
La Forge, William C.  
Lau, Michael W.  
MacInnis, Douglas N.  
Mailman, Richard H.  
May, Lewis H. V.  
Mazur, Murray H.  
McCleary, Jack E.  
Miller, Richard D.  
Milliken, Ralph M.  
Morgan, Henry G.  
Murieta, A. J., Jr.  
Neuenschwander, Robert S.  
Noguchi, Thomas T.  
Olch, David I.  
Parlour, Richard R.  
Payne, J. Howard  
Penka, Ernest J.  
Penn, Sidney W.  
Pettit, Richard D.  
Pollack, John V.  
Quinn, William F.  
Richards, Melvin  
Roberts, James C., Jr.  
Rosenberg, Irving G.  
Sakaeuchi, Sambo S.  
Senseman, W. R.  
Shearer, S. K.  
Smith, Thayer A.  
Starr, Harvey E.  
Stauffer, Floyd R.  
Stragell, Robert  
Sullivan, Richard A.  
Taw, Richard L.  
Trumbull, William E.  
Turrill, Fred L.  
Voigt, Philip F.  
Walter, LeRoy E.  
Watson, Robert L., Jr.  
Weil, William S.  
Weiss, Murray J.  
Westerbeck, Charles W.  
Winter, Edward J.  
Woolington, Sam S.  
Wunderlich, Edwin E.  
Zinn, Alexander N.  
Zinn, Willard J.

### MARIN (4)

Ablin, Arthur R.  
Jaros, Duval  
Manwaring, John  
McGee, John

### MENDOCINO-LAKE (2)

Roherson, B. B.  
Waring, William W.

### MERCED-MARIPOSA (2)

Anclin, John V.  
Faber, Dorian

### MONTEREY (3)

Hull, Osman H.  
Klinefelter, Robert P.  
Turner, Joseph E.

### Alternates

Condit, Leonard O.  
Covell, David G.  
Cronin, John F.  
Dahlquist, Joseph G.  
Dasche, Alfred M.  
Davies, William Dean  
Del Junco, Tirso  
Duemler, Louis P.  
Edwards, Arthur F.  
Erickson, James F.  
Feisberg, Munish  
Fischer, Barton L.  
Fortier, John J.  
Freidin, Morris  
Fritz, Samuel H.  
Gaal, Peter G.  
Grant, Robert A.  
Greco, Donald J.  
Gregg, David W.  
Haines, Charles L., Jr.  
Hardin, Byron  
Hoffman, Eugene F., Sr.  
Hoffman, Peter L.  
Japencza, Jack W.  
Kneerle, Rudolph E.  
Kaminski, Kenneth L.  
Kaufmann, Bertram Jr.  
Keller, Thomas B.  
Kelley, Walter W.  
Kern, William H.  
Lyons, John G.  
Klein, E. Philip  
Korn, Bernard J.  
Knett, Michael  
Latshaw, Charles W.  
Lefevre, Timothy M.  
Lopez, Charles J.  
Marcus, Stanley  
Martyn, Donald G.  
Massey, Ben D., Jr.  
McCandless, Harrison C.  
McElwee, Charles B.  
McLaughlin, Henry M.  
Michels, Arthur G.  
Miller, Woodrow  
Moshein, Jack  
Murray, Gregory C.  
Nishizawa, Akira  
Ofoni, Eugene R.  
Osher, Eugene M.  
Palmer, Robert H.  
Perkins, Raymond C.  
Picklester, James C.  
Rayman, Irving B.  
Redewill, Francis H., Jr.  
Riffenburgh, Ralph S.  
Rodgers, Victor A.  
Rosenkrans, Donald R., Jr.  
Rothenberg, Sanford F.  
Rubin, Henry J.  
Rudy, Norman E.  
Ryerson, F. Stuart  
Smiley, Douglas F.  
Smith, Laurence J.  
Summers, L. F.  
Tashma, Albert  
Thom, John G.  
Titus, Edward D.  
Todd, William H.  
Toft, Jack C.  
Turcillo, Joseph, Jr.  
Vogel, Philip J.  
Wallen, E. Robert  
Weiss, Benjamin J.  
Wieton, John R.  
Wone, Thomas A.  
Woolley, Morton M.  
(1 vacancy)

Lee, John R.  
Strathairn, T. Scott  
Tavel, Frank  
White, A. Halman

Joyce, Donald G.  
Nicholson, Thomas A.

Kreps, Roland  
Soderstrom, Edwin

Eldredge, Eugene E.  
Elliott, Thomas S.  
Kandlbinder, A. F.

### Delegates

#### NAPA (2)

Brignoli, Walter H.  
Ledwich, Thomas W.

#### ORANGE (15)

Altman, Richard F.  
Ball, Dexter T.  
Carroll, Vincent P.  
Gerrie, Wallace A.  
Graham, Ralph E.  
Hawkins, G. William  
Kay, Fred M.  
Martin, Walter H.  
Mosier, Laurance A.  
Paul, Carl J.  
Plumb, Hugh J., Jr.  
Price, J. B.  
Schneider, Shirley M.  
Stonestreet, Marshall  
Thompson, Arthur F.

#### PLACER-NEVADA (2)

Becker, Bruce  
Johnson, F. Harold

#### RIVERSIDE (5)

Ivanoff, John C.  
Lyons, John G.  
Silver, Harrison E.  
Stone, H. H.  
Zweig, Robert M.

#### SACRAMENTO (8)

Babich, John  
Berg, John A.  
Berman, A. E.  
Cook, Orrin S.  
Farley, James O.  
Martin, James  
Pope, Glenn A.  
Terry, Daniel W.

#### SAN BENITO (2)

Brooks, Fisk  
Telfer, James

#### SAN BERNARDINO (7)

Halburg, Clarence T.  
Hendrickson, M. A.  
Malone, Frank  
Miano, Bro D. A.  
Sprague, Charles P.  
Sterling, Allen F.  
Wake, Donald K.

#### SAN DIEGO (15)

Brimbaugh, Simon C.  
Carpenter, Walter F.  
Hippen, Robert L.  
Hokr, William K.  
Isenhour, Roger C.  
King, Ralph M.  
Kirtland, Howard  
Messenger, Harold  
Peck, J. Haddon A., Jr.  
Peck, Sam  
Plumb, Robert T.  
Rumsey, John M.  
Tancredi, Chester  
Telford, Joseph W.  
Youel, Milo A.

#### SAN FRANCISCO (20)

Baer, Charlotte C.  
Barrios, Xavier O.  
Bender, William T.  
Biskind, Gerson R.  
Bonfilio, Nicholas D.  
Coleman, Arthur H.  
Feldman, Sanford E.  
Fullenlove, Tom M.  
Gibbons, Henry, III  
Herzog, George K., Jr.  
Lee, Jane P.  
Pevchouse, Byron C.  
Pillsbury, Philip  
Rixford, Emmet L.  
Robinson, Saul J.  
Saunders, John B. de C. M.  
Schaffartzik, Ralph W.  
Schaupe, Willis G.  
Scholten, Paul  
Wayburn, Edgar

### Alternates

Ehrlich, Harry  
Murray, Dwight H., Jr.

Andrews, Alan V.  
Bouchelle, McLemore  
Burrill, C. William  
Donaldson, A. Norton  
Geddes, David K.  
Hastings, Charles M.  
Higger, Harvey L.  
Kammerman, Richard F.  
Llewellyn, Gene A.  
McFarland, Philip H.  
Neu, Robert E.  
Plows, Charles W.  
Voge, Lyle C.  
Wightman, Ardath H.  
(1 vacancy)

Anthony, William A., Jr.  
Sweeney, George H.

Borak, Peter J.  
Kinney, William  
Lansing, J. Dee  
Pitchford, Clyde A.  
Shumway, Ord L.

Fong, William  
Janushkowsky, Alex  
Lawrence, W. Sherwood  
O'Kane, Calvin R.  
Quillinan, Robert  
Reilly, Philip J.  
Shaffrath, Max  
Stanford, Roy

Kirch, Joseph  
Quinn, Robert D.

Ballard, Ross L.  
Carmack, Charles  
Cillespie, James  
Harer, W. Rowson, Jr.  
Jernigan, Shelly  
Judd, Richard  
(1 vacancy)

Bartel, Robert M.  
Cowell, William E.  
Dill, Donald  
Elliott, Gladden V.  
Feenev, Michael J.  
Heard, Jerome L.  
Herrick, William C.  
Orr, Rex  
Peabody, Homer D., Jr.  
Reck, Lawrence E.  
Shumacher, Alan E.  
Smith, Sam W.  
Tielale, William  
Tullik, Richard II.  
Wells, John J.

Bovill, Edward G., Jr.  
Bryan, John R.  
Cohn, Bradford  
Cook, Robert E.  
Driscoll, John A.  
Erskine, John M.  
Gorney, Mark  
Hopp, Eugene S.  
Kelley, Edward T.  
King, Charles D.  
Miller, Charles F.  
Musser, Don C.  
Noble, W. Morris H.  
Paver, Robert L.  
Sachs, David D.  
Sirbu, Abraham B.  
Solari, Rafael A.  
Tipton, Dale L.  
Wellington, C. J.  
Williams, A. Justin



<i>Delegates</i>	<i>Alternates</i>	<i>Delegates</i>	<i>Alternates</i>
<b>SAN JOAQUIN (4)</b> Benn, James J. McNally, John Salter, Robert K. Williams, George	Clark, Stanley A., Jr. Morozumi, John Talley, Robert Wass, Warren	<b>STANISLAUS (3)</b> Nelson, William New, David J. Purvis, Robert	Bigelow, Wayne B. Galbraith, Nicoll Pote, William W.
<b>SAN LUIS OBISPO (2)</b> Chambers, James R. Fryer, Harry J., Jr.	Cletsoway, R. W. Warren, L. H.	<b>TEHAMA (2)</b>	
<b>SAN MATEO (7)</b>		<b>TULARE (2)</b> Goettle, James W. Lavers, George D.	Bingham, Gary P. McConnaughey, Hal D.
<b>SANTA BARBARA (5)</b> Blanchard, John P. McNiece, Kenneth Miles, Harold Rutten, R. John Ziemba, Joseph	Dahlen, Gregory A. Dietrich, Sanford R. Elam, Eldon Feldsted, E. T. Owens, Daniel E.	<b>VENTURA (4)</b> Cstettenbauer, Joseph F. Hair, Charles M. Huff, W. Cloyce Rulfo, Henry J.	Johnston, D. Gordon Mathews, Albert L. Sherrill, Glenn D. Stoutz, Henry L.
<b>SANTA CLARA (14)</b> Armstrong, Frederick S. Boice, Clyde L. English, Leo Fox, Leon P. Giansiracusa, Frank Grossman, Maurice Kaufman, S. Fred Lee, R. Hewlett Liston, Edward McCort, James J. O'Neill, Robert J. Rowles, Donald Scarborough, C. Gerald Zoglin, Stanton	Bonar, Samuel Burnett, Robert Corsiglia, Victor F., Jr. Drinker, Henry Elliott, Hugh Hake, Dexter Houck, George Munemitsu, Saylo Nola, Vincent F. Parker, Malcolm Schade, Hugh Upton, Hubert M. Vincent, Paul J. Whelan, Harry G.	<b>YOLO (2)</b> Werblun, Merrill Wilson, B. Kent	Dawkins, C. Edward Young, Corbin A.
<b>SANTA CRUZ (3)</b> DePuy, J. L. Jones, Robert W. Nelson, Carl	Jones, Robert C. King, John W. Mahaney, John G.	<b>YUBA-SUTTER-COLUSA (2)</b>	
<b>SHASTA-TRINITY (2)</b> Martin, George A. Polka, Michael G.	Keye, John, Jr. Peterson, R. Eugene	<b>EX-OFFICIO SCIENTIFIC BOARD (18)</b> Belford, William W. Bettman, Jerome W. Bittner, Donald L. Brockman, Seymour J. Cobb, Dudley M. Dillon, John B. Gonda, Thomas A. Grayson, Charles E. Hockwald, Robert S. Jones, Ellis W. Kaye, Ronald Maibach, Harold I. Meleyco, Leo N. Pearman, Robert O. Richards, Victor Rubin, David Russell, Keith P. Stein, Justin J.	Halter, Bert L. Wood, David A.
<b>SISKIYOU (2)</b>		<b>EX-OFFICIO PAST PRESIDENTS (22)</b> Peers, Robert A. . . . . 1935 Molony, William R., Sr. . . . 1942 Schaupp, Karl L., Sr. . . . . 1943 Cline, John W. . . . . 1947 Askey, E. Vincent. . . . . 1948 Cass, Donald . . . . . 1950 MacLean, H. Gordon. . . . . 1951 Green, John W. . . . . 1953 Morrison, Arlo A. . . . . 1954 Shipman, Sidney J. . . . . 1955 MacDonald, Frank A. . . . . 1957	West, Francis E. . . . . 1958 Reynolds, T. Eric. . . . . 1959 Foster, Paul D. . . . . 1960 Bostick, Warren L. . . . . 1961 Wheeler, Omer W. . . . . 1962 Sherman, Samuel R. . . . . 1963 Doyle, James C. . . . . 1964 Teall, Ralph C. . . . . 1965 MacLaggan, James C. . . . . 1966 Morrison, John G. . . . . 1967 Todd, Malcolm C. . . . . 1968
<b>SOLANO (2)</b> Gullock, Alvin H. Vincent, Keith	Miller, John C. Olson, William J.	<b>EX-OFFICIO HONORARY PAST PRESIDENTS (2)</b> Murray, Dwight H. Wilbur, Dwight L.	
<b>SONOMA (3)</b> Butler, Robert H. Craven, Wayne M. Dunn, William J.	Anderson, Raymond C. Clary, David Lones, Frank E.		

# House of Delegates • 1970 Annual Session

## AGENDA

*Speaker* ..... William F. Quinn, Los Angeles  
*Vice-Speaker* ..... Joseph F. Boyle, Los Angeles  
*Secretary* ..... Helen B. Weyrauch, San Francisco

**FIRST MEETING, Saturday, March 7, 1970**

**REGISTRATION—3 p.m.**

**MEETING STARTS—4 p.m. SHARP**

1. Call to order.
2. Announcement of Reference Committees and Miscellaneous Announcements.
  - (a) Committee on Credentials. (Delegates must register with the Committee.)
  - (b) Reference Committee on Community and Environmental Health. (Reference Committee A.)
  - (c) Reference Committee on Government Medical Programs. (Reference Committee B.)
  - (d) Reference Committee on Medical Economics, Insurance and Prepayment. (Reference Committee C.)
  - (e) Reference Committee on Scientific and Educational Activities. (Reference Committee D.)
  - (f) Reference Committee on Public and Professional Relations. (Reference Committee E.)
  - (g) Reference Committee on Finance. (Reference Committee F.)
  - (h) Reference Committee on Constitution and Bylaws. (Reference Committee G.)
  - (i) Reference Committee on California Blue Shield. (Reference Committee H.)
3. Honored Guests.
  - (a) Fifty-year Members.
  - (b) Past Presidents.
  - (c) Allied Health Groups.
  - (d) SAMA Students.
4. Report of Committee on Credentials, and Organization of the House of Delegates—Roll Call.
5. Recognition of President of the Woman's Auxiliary to the CMA—Mrs. Edmund Mahon.
6. Address by President—Albert G. Miller.
7. Report of the President—Albert G. Miller.
8. Report of the President-Elect—Ralph W. Burnett.
9. Report of the Speaker and Vice-Speaker of the House of Delegates—William F. Quinn and Joseph F. Boyle.
10. Report of the Trustees of the California Medical Association—Albert G. Miller.
11. Report of Physicians' Benevolence Fund, Inc.—Albert G. Miller.
12. Report of the Secretary—Helen B. Weyrauch.
13. Report of the Editor—Malcolm S. M. Watts.
14. Report of the Executive Director—Robert L. Thomas.
15. Report of Legal Counsel—Hassard, Bonnington, Rogers & Huber.
16. Report of the Executive Committee—Albert G. Miller.
17. Report of the Council—Harold Kay, Chairman.
18. Report of California Blue Shield Trustees—Carl E. Anderson, Chairman, Board of Trustees.
19. Reports of Commissions.
  - (a) Commission on Medical Services — Arthur F. Howard, Fresno.
  - (b) Commission on Public Agencies — Joseph P. O'Connor, Pasadena.
  - (c) Commission on Community Health Services — Marvin J. Shapiro, Encino.
  - (d) Commission on Communications — Elmer F. Goel, Beverly Hills.
  - (e) Commission on Professional Welfare—George K. Herzog, Jr., San Francisco.
  - (f) Judicial Commission—Francis E. West, Downey.
  - (g) Commission on Allied Health Professions and Services — Lewis T. Bullock, Los Angeles.
  - (h) Commission on Hospital Affairs — John T. Saidy, San Mateo.
  - (i) Scientific Board — Charles J. Tupper, Davis.
20. Reports of Other Committees.
  - (a) Bureau of Research and Planning — Henry V. Eastman, Tustin.
  - (b) Role of Medicine in Society — Malcolm S. M. Watts, San Francisco.
  - (c) Organizational Review & Planning — E. Kash Rose, Napa.
  - (d) Committee on Legislation — Malcolm C. Todd, Long Beach.
  - (e) Finance Committee — Harold Kay, Oakland.
  - (f) Medical Executives Conference — Clark J. Donmyer, San Bernardino.
  - (g) Delegates to the AMA — Eugene F. Hoffman, Sr., Los Angeles.
21. Old and Unfinished Business.
22. New Business.
23. Adjournment.

### CALPAC REPORTS

Immediately Following the Opening Session  
of the CMA House of Delegates

(To be recessed and reconvened at 9:00 a.m. Wednesday, March 11)

### ORDER OF BUSINESS

1. Call to order.
2. Supplemental report of Credentials Committee—Roll Call.
3. Introduction of President-Elect of Women's Auxiliary—Mrs. Kenneth McNiece.
4. Address by President-Elect—Ralph W. Burnett.
5. Secretary's announcement of Council's selection of time and place for the 1971 Annual Session.
6. Election of Officers:
  - (a) President-Elect.
  - (b) Speaker.
  - (c) Vice-Speaker.
  - (d) Councilors (three-year terms):
    - (1) First District — Stanley A. Moore, San Diego (term expiring).
    - First District — Imperial and San Diego Counties.
    - (2) Third District — Henry V. Eastman, Tustin (term expiring).
    - Third District — Orange County.
    - (3) Fourth District — Office No. 3 — Homer C. Pheasant, Los Angeles (term expiring).
    - (4) Fourth District — Office No. 6 — Marvin J. Shapiro, Encino (term expiring).
    - (5) Fourth District — Office No. 9 — Frank A. Rogers, Whittier (term expiring).
    - Fourth District — Los Angeles County.
    - (6) Fifth District—Joseph F. Maguire, Ventura (term expiring).
    - Fifth District—San Luis Obispo, Santa Barbara and Ventura Counties.
    - (7) Seventh District — Office No. 1 — Daniel W. Clark, San Jose (term expiring).
    - Seventh District — Monterey, San Benito, San Mateo, Santa Clara and Santa Cruz Counties.
    - (8) Eighth District—Office No. 2—Roberta Fenlon, San Francisco (term expiring).
    - Eighth District—San Francisco County.
    - (9) Ninth District — Office No. 2 — Frederick Ackerman, Pleasant Hill (term expiring).
    - Ninth District—Alameda and Contra Costa Counties.
    - (10) Tenth District—E. Kash Rose, Napa (term expiring).
    - Tenth District—Del Norte, Humboldt, Lake Marin, Mendocino, Napa, Solano and Sonoma Counties.
  - (e) Delegates to the American Medical Association: (Delegates and Alternates to the American Medical Association are elected for terms of two calendar years. The Delegates and Alternates to be elected at this meeting will serve for two calendar years starting January 1, 1971, except as otherwise noted.)
    - (1) John G. Morrison, San Leandro (term expiring).
    - (2) William F. Quinn, Los Angeles (term expiring).
    - (3) Robert C. Combs, Irvine (term expiring).
    - (4) Homer C. Pheasant, Los Angeles (term expiring).
    - (5) Alfred J. Murrieta, Los Angeles (term expiring).
    - (6) Leon P. Fox, San Jose (term expiring).
    - (7) Arlo A. Morrison, Ventura (term expiring).
    - (8) James E. Feldmayer, Exeter (term expiring).
    - (9) O. W. Wheeler, Riverside (term expiring).
    - (10) Malcolm C. Todd, Long Beach (term expiring).
    - (11) J. E. Vaughan, Bakersfield (term expiring).
    - (12) Carl E. Anderson, Santa Rosa (term expiring).
  - (f) Election of Alternate to fill unexpired term of Richard S. Wilbur (alternate to Leon P. Fox) for year 1970.
  - (g) Alternates to the American Medical Association: (Terms of all incumbents expiring. All offices for two year terms starting January 1, 1971, except as otherwise noted.)
    - (1) Frederick Ackerman, Pleasant Hill (alternate to Samuel R. Sherman).
    - (2) H. Russell Fisher, Glendale (alternate to William F. Quinn).
    - (3) Frank A. Rogers, Whittier (alternate to Robert C. Combs).
    - (4) James C. MacLaggan, San Diego (alternate to Homer C. Pheasant).
    - (5) Harold Kay, Oakland (alternate to Alfred J. Murrieta).
    - (6) Richard S. Wilbur, Palo Alto (alternate to Leon P. Fox).
    - (7) Henry Brown, San Mateo (alternate to Arlo A. Morrison).
    - (8) Charles Grayson, Sacramento (alternate to James E. Feldmayer).
    - (9) Wilbur Bailey, Los Angeles (alternate to O. W. Wheeler).
    - (10) Neil C. Hamel, Encino (alternate to Malcolm C. Todd).
    - (11) Joseph P. O'Connor, Pasadena (alternate to J. E. Vaughan).
    - (12) Jean F. Crum, Downey (alternate to Carl E. Anderson).
7. Election of California Blue Shield Trustees (three-year terms): Report of CMA Council as Nominating Committee.



Incumbents, terms expiring:

Mr. Richard W. Hackler, San Francisco  
Mr. Frank R. McDougall, Los Angeles  
Harold M. Messenger, M.D., San Diego  
Mr. C. E. Pigg, Van Nuys  
Richard S. Wilbur, M.D., Palo Alto

8. Announcement by Secretary.  
Council's nominations of members of Commissions and Committees. (For approval by the House of Delegates.)
9. Reports of Reference Committees:
  - (a) Report of Reference Committee A on Community and Environmental Health.
  - (b) Report of Reference Committee B on Government Medical Programs.
  - (c) Report of Reference Committee C on Medical Economics, Insurance and Prepayment.
  - (d) Report of Reference Committee D on Scientific and Educational Activities.

- (e) Report of Reference Committee E on Public and Professional Relations.
- (f) Report of Reference Committee F on Finance.
- (g) Report of Reference Committee G on Constitution and Bylaws.
- (h) Report of Reference Committee H on California Blue Shield.

10. Unfinished Business.

11. New Business.

12. Presentation of Officers:

President—Presentation of Plaque to President Albert G. Miller.  
President-Elect.  
Speaker.  
Vice-Speaker.

13. Approval of Minutes. (Committee to edit.)

14. Adjournment.

WILLIAM F. QUINN, *Speaker*  
HELEN B. WEYRAUCH, *Secretary*

## Constitutional Amendment

### FOR ACTION IN 1970

One Constitutional amendment was introduced in the 1969 House of Delegates and, under the terms of the Constitution, must lie on the table until the next regular meeting of the House of Delegates.

This proposed amendment is shown here for the information of the membership. In addition, the proposed Constitutional amendment is required to be printed in two issues of CALIFORNIA MEDICINE before it comes before the House of Delegates for action.

SCIENTIFIC BOARD REPRESENTATION ON  
COUNCIL, ARTICLE III, PART B, SECTION 9(d)  
Constitutional Amendment 1-69 Committee G  
Introduced by: Richard S. Wilbur, M.D.  
Representing: The Council

*Resolved:* That Article III, Part B, Section 9(d) of the Constitution of this Association be amended by deleting

the language in parentheses, so that this section shall read:

(d) The secretary and editor, when they are members of the Association, (and one member of the Executive Committee of the Scientific Board, who shall be elected by the Executive Committee of that body from representatives of the scientific sections or members at large. These three persons) shall be ex officio members of the Council without the right to vote.

And be it further

*Resolved:* That a new subsection (e) be added, which shall read: (New words in italics.)

(e) *One member of the Executive Committee of the Scientific Board, who shall be elected by the Scientific Board from representatives of the scientific sections or members-at-large, who shall be an ex officio member of the Council with the right to vote.*

*ACTION:* Tabled for one year. To be acted upon at the 1970 meeting of the House of Delegates.

Reports of officers, commissions and committees of the California Medical Association, together with more detailed audited financial statements for the fiscal year ended June 30, 1969, are printed in the Annual Report Bulletin, which is distributed to Delegates and Alternates at the meeting of the

House of Delegates. The Bulletin is also available to any member of the Association on request directed to Robert L. Thomas, Executive Director, California Medical Association, 693 Sutter Street, San Francisco, California 94102.

#### **REPORT OF**

#### ***Certified Public Accountants***

#### **CALIFORNIA MEDICAL ASSOCIATION:**

We have examined the balance sheets of California Medical Association and Trustees of California Medical Association at June 30, 1969, and the related statements of income and expenses for the year then ended. Our examinations were made in accordance with generally accepted auditing standards, and accordingly included such tests of the accounting records and such other auditing procedures as we considered necessary in the circumstances.

In our opinion, the statements referred to above present fairly the financial position of California Medical Association and Trustees of California Medical Association at June 30, 1969, and the results of their operations for the year then ended, in conformity with generally accepted accounting principles applied on a basis consistent with that of the preceding year.

**JOHN F. FORBES & COMPANY**

San Francisco, California  
August 15, 1969

## **FINANCIAL REPORTS**

### **CALIFORNIA MEDICAL ASSOCIATION AND TRUSTEES OF THE CALIFORNIA MEDICAL ASSOCIATION**

#### **CALIFORNIA MEDICAL ASSOCIATION:**

Balance Sheet, June 30, 1969 and 1968, and Comparison  
Excess of Assets over Liabilities, June 30, 1969 and 1968, and Comparison  
Statement of Income and Expenses Year Ended June 30, 1969

#### **TRUSTEES OF THE CALIFORNIA MEDICAL ASSOCIATION:**

Balance Sheet, June 30, 1969 and 1968, and Comparison  
Statement of Income and Expenses Years Ended June 30, 1969 and 1968, and  
Comparison

#### **CALIFORNIA MEDICAL ASSOCIATION AND TRUSTEES OF THE CALIFORNIA MEDICAL ASSOCIATION:**

Notes to Financial Statements

**CALIFORNIA  
MEDICAL  
ASSOCIATION**

(A Nonprofit Association)

 Balance Sheet  
June 30, 1969  
and 1968  
and Comparison

	JUNE 30		Increase (Decrease)
	1969	1968	
ASSETS			
CASH .....	\$ 62,425	\$ 93,963	\$ (31,538)
CERTIFICATE OF DEPOSIT— CROCKER-CITIZENS NATIONAL BANK .....		500,000	(500,000)
UNITED STATES TREASURY BILLS, AT COST .....	1,081,894	493,497	588,397
ACCOUNTS RECEIVABLE, NET .....	86,041	77,740	8,301
ACCRUED INTEREST .....	6,297	3,995	2,302
NOTES RECEIVABLE:			
Central California Blood Bank .....	71,000	71,000	
Other .....	3,200	4,000	(800)
	74,200	75,000	(800)
PREPAID EXPENSES AND OTHER ASSETS:			
Retirement program premium (Note 1) .....	17,530	19,054	(1,524)
Insurance .....	2,880	3,218	(338)
Deposits .....	4,383	3,549	834
Other .....	3,424	1,224	2,200
Total prepaid expenses and other assets .....	28,217	27,045	1,172
OFFICE FURNITURE AND EQUIPMENT (Note 2) .....	46,375	34,439	11,936
NOTE AND ACCOUNTS RECEIVABLE, AFFILIATED ORGANIZATIONS:			
Trustees of the California Medical Association:			
Demand note, with interest at 4% per year .....	125,000	125,000	
Account receivable .....	3,140	2,170	970
	128,140	127,170	970
Accounts receivable:			
Six Ninety Three Sutter Publications, Inc. ....		3,470	(3,470)
California Medical Education and Research Foundation, Inc. ....	22,843	2,887	19,956
Other .....	1,331	550	781
Total notes and accounts receivable, affiliated organizations .....	152,314	134,077	18,237
	<u>\$1,537,763</u>	<u>\$1,439,756</u>	<u>\$ 98,007</u>
LIABILITIES			
ACCOUNTS PAYABLE:			
American Medical Association .....	\$ 23,310		\$ 23,310
American Medical Education Foundation .....	27,865	\$ 81,688	(53,823)
Other .....	62,556	90,757	(28,201)
Total accounts payable .....	113,731	172,445	(58,714)
DUE TO AFFILIATED ORGANIZATIONS:			
Physicians' Benevolence Fund .....	22,441		22,441
Six Ninety Three Sutter Publications, Inc. ....	3,379		3,379
Total due to affiliated organizations .....	25,820		25,820
DEFERRED INCOME:			
Dues and subscriptions applicable to the succeeding fiscal year .....	962,110	917,196	44,914
Other .....	417	863	(446)
Total deferred income .....	962,527	918,059	44,468
Total liabilities .....	1,102,078	1,090,504	11,574
EXCESS OF ASSETS OVER LIABILITIES (Note 3) .....	435,685	349,252	86,433
	<u>\$1,537,763</u>	<u>\$1,439,756</u>	<u>\$ 98,007</u>

See notes to financial statements.



**CALIFORNIA  
MEDICAL  
ASSOCIATION**

	JUNE 30		Increase (Decrease)
	1969	1968	
UNRESTRICTED:			
Balance at beginning of year. . . . .	\$233,531	\$157,210	\$ 76,321
Excess of income over expenses for the year. . . . .	86,433	192,042	(105,609)
Transfer to restricted. . . . .	43,217	115,721	(72,504)
	43,216	76,321	(33,105)
Balance at end of year. . . . .	276,747	233,531	43,216
RESTRICTED AS TO USE (Note 4):			
Balance at beginning of year. . . . .	115,721		115,721
Transfer from excess of income over expenses. . . . .	43,217	115,721	(72,504)
Balance at end of year. . . . .	158,938	115,721	43,217
Total. . . . .	\$435,685	\$349,252	\$ 86,433

See notes to financial statements.

Excess of Assets  
Over Liabilities  
June 30, 1969  
and 1968, and  
Comparison

<b>INCOME:</b>		
Membership dues, less portion allocated to subscriptions to CALIFORNIA MEDICINE.....	\$1,894,894	
Booth rentals at Annual Session.....	39,930	
Fees, postgraduate courses.....	19,690	
Fee for collection of American Medical Association dues.....	15,688	
Interest earned.....	55,114	
Other .....	2,529	
Total income .....		\$2,027,845
<b>EXPENSES:</b>		
Physicians' Services and Programs.....	290,106	
Divisional Programs .....	1,266,056	
General expenses .....	293,085	
	1,849,247	
Contributions .....	78,306	
Excess of expenses over income—CALIFORNIA MEDICINE.....	13,859	
Total .....		1,941,412
Excess of income over expenses.....		\$ 86,433

See notes to financial statements.

Statement of Income  
and Expenses  
Year Ended  
June 30, 1969

**TRUSTEES OF THE  
CALIFORNIA  
MEDICAL  
ASSOCIATION**  
(A Nonprofit Corporation)

Balance Sheet,  
June 30, 1969  
and 1968, and  
Comparison

	JUNE 30		Increase (Decrease)
	1969	1968	
ASSETS			
CASH	\$ 46,058	\$ 25,701	\$ 20,357
UNITED STATES TREASURY BONDS, AT COST (Maturity value, \$1,121,000; market value, 1969, \$996,507 and 1968, \$1,014,616)	1,119,152	1,119,152	
NOTE AND ACCOUNTS RECEIVABLE	795	6,017	(5,222)
ACCRUED INTEREST	2,119	2,119	
INVESTMENTS IN WHOLLY-OWNED SUBSIDIARIES, AT COST:			
Pacific Magnetic Tape Co. (Note 5)	9,000	9,000	
Six Ninety Three Sutter Publications, Inc.	1,000	1,000	
Total investments in wholly-owned subsidiaries	10,000	10,000	
PROPERTIES, AT COST (Note 6):			
Buildings and improvements	406,805	392,800	14,005
Carpets, installation, and other	19,026	8,575	10,451
	425,831	401,375	24,456
Less accumulated depreciation	118,631	99,501	19,130
	307,200	301,874	5,326
Land	180,217	180,217	
	487,417	482,091	5,326
EQUIPMENT, AT NOMINAL VALUE	1	1	
CASH SURRENDER VALUE OF LIFE INSURANCE (Note 7)	51,391	46,080	5,311
PREPAID INSURANCE	1,086	1,458	(372)
	<u>\$1,718,019</u>	<u>\$1,692,619</u>	<u>\$ 25,400</u>
LIABILITIES			
ACCOUNTS PAYABLE AND ACCRUED EXPENSES:			
California Medical Association	\$ 3,140	\$ 1,319	\$ 1,821
Interest and accrued expenses	3,499	3,004	495
Total accounts payable and accrued expenses	6,639	4,323	2,316
NOTES PAYABLE:			
California Medical Association, payable on demand, with interest at 4% per year—Unsecured	125,000	125,000	
The Connecticut Mutual Life Insurance Company, with deed of trust as collateral (payable in quarterly installments of \$2,506, including interest at 4¼% per year, to March 1, 1973) (Note 6)	32,014	40,452	(8,438)
Total notes payable	157,014	165,452	(8,438)
TRUST FUNDS (Note 7)	134,587	125,127	9,460
DEFERRED COMPENSATION PAYABLE	16,800	16,750	50
DEFERRED INCOME	760	753	7
EXCESS OF ASSETS OVER LIABILITIES (Note 3):			
Balance at beginning of year	1,380,214	1,349,129	31,085
Excess of income over expenses for the year	22,005	31,085	(9,080)
Balance at end of year	<u>1,402,219</u>	<u>1,380,214</u>	<u>22,005</u>
	<u>\$1,718,019</u>	<u>\$1,692,619</u>	<u>\$ 25,400</u>

See notes to financial statements.

Statement of Income  
and Expenses  
Years Ended  
June 30, 1969  
and 1968, and  
Comparison

	YEAR ENDED JUNE 30		Increase (Decrease)
	1969	1968	
INCOME:			
Excess of rental income over property expenses.....	\$ 3,650	\$13,833	\$(10,183)
Interest on United States Treasury bonds.....	29,000	29,000	
Dividend—Pacific Magnetic Tape Equipment Co.....		900	(900)
Miscellaneous .....		52	(52)
	32,650	43,785	(11,135)
EXPENSES (other than property)—			
Fees and insurance.....	4,090	2,736	1,354
	28,560	41,049	(12,489)
OTHER CHARGES—PROVISION FOR RETIREMENT OR OTHER BENEFITS OF EMPLOYEES OF AN AFFILIATED ORGANIZA- TION .....			
	6,555	9,964	(3,409)
EXCESS OF INCOME OVER EXPENSES FOR THE YEAR .....	\$22,005	\$31,085	\$(9,080)

See notes to financial statements.

## NOTE:

## 1. EMPLOYEE PENSION PLANS

In addition to the Group Pension Program which became effective on January 1, 1961, the California Medical Association has arranged for the funding of a Past Service Pension Plan for certain full-time employees which resulted in an additional liability of \$62,734. This liability is being amortized over 20 years from January 1, 1966. The Travelers' Insurance Company has underwritten the plan and will furnish annuity contracts as eligible employees retire. Because the current service benefits and all of the benefits for retired employees have already been purchased under the contract, there is a liability only for the unfunded value of vested benefits. This liability amounted to \$16,750 on January 1, 1969. This amount is not recorded on the books of the Association nor included in the accompanying balance sheet.

The pension expense for the year was \$39,903. This expense is determined by the underwriter each year, and may vary, depending on new qualifying employees, and credits arising from qualifying employees leaving the Association.

## 2. OFFICE FURNITURE AND EQUIPMENT—CALIFORNIA MEDICAL ASSOCIATION

Acquisitions prior to July 1, 1966 are carried at a nominal amount of \$1. At May 13, 1966, the firm of Marshall and Stevens, appraisers, estimated that the sound value of assets then owned was \$104,415. Assets acquired after July 1, 1966 are summarized as follows:

	Cost	Depreciation or Amortization
Office furniture and equipment:		
Owned July 1, 1968.....	\$39,602	\$ 8,224
Purchased during the current year.....	21,890	
Provision for the current year.....		8,769
	<u>61,492</u>	<u>16,993</u>
Leasehold improvements, Sacramento office:		
Cost.....	3,357	
Amortization.....		1,481
	<u>\$64,849</u>	<u>\$18,474</u>
Net book value.....	<u>\$46,375</u>	

## 3. COMBINED NET WORTH

The Trustees of the California Medical Association is a wholly-owned subsidiary of the California Medical Association. The Trustees hold in trust a large portion of the assets utilized by the California Medical Association. The combined net worth of the two organizations is summarized as follows:

Entity	JUNE 30		Increase
	1969	1968	
California Medical Association:			
Restricted as to use.....	\$ 158,938	\$ 115,721	\$ 43,217
Unrestricted.....	276,747	233,531	43,216
	435,685	349,252	86,433
Trustees of the California Medical Association.....	1,402,219	1,380,214	22,005
	<u>\$1,837,904</u>	<u>\$1,729,466</u>	<u>\$108,438</u>

The combined net worth at June 30, 1969 shown in the summary above does not include the following items:

## California Medical Association:

Excess of the appraised value of furniture and office equipment acquired prior to July 1, 1968 over accumulated depreciation and nominal carrying value, approximately..... \$ 72,600

Audio-Digest Foundation, a wholly-owned subsidiary; net worth as shown by the Foundation's audited balance sheet at June 30, 1969..... 353,869

426,469

## Trustees of the California Medical Association—Excess of net worth over Trustees' investment

in their wholly-owned subsidiary, Pacific Magnetic Tape Co., based on that company's unaudited balance sheet at June 27, 1969..... 47,933

\$474,402

## 4. EXCESS OF ASSETS OVER LIABILITIES—RESTRICTED AS TO USE

The budget for the fiscal year ended June 30, 1968, as approved by the Council, authorized the segregation of a portion of the excess of income over expenses in the amount of \$115,721, leaving the remainder available for possible current requirements. For the fiscal year ended June 30, 1969, the amount of \$43,217 was added to the restricted balance. This addition represents one-half of the excess of income over expenses for this year.

## 5. WHOLLY-OWNED SUBSIDIARY

The Trustees of the California Medical Association owns all of the outstanding stock of the Pacific Magnetic Tape Equipment Co., which was formed for the purpose of merchandising magnetic tape equipment as an adjunct to the activities of the Audio-Digest Foundation, a wholly-owned subsidiary of the California Medical Association.

CALIFORNIA MEDICAL  
ASSOCIATION and  
TRUSTEES OF THE  
CALIFORNIA MEDICAL  
ASSOCIATION

Notes to  
Financial Statements



## 6. PROPERTIES

The properties held by the Trustees of the California Medical Association are summarized as follows:

	693 Sutter Street	679 Sutter Street	Total
Buildings and improvements .....	\$328,917	\$ 77,889	\$406,806
Carpets, installation, and other .....	18,356	670	19,026
	<u>347,273</u>	<u>78,559</u>	<u>425,832</u>
Less accumulated depreciation .....	108,045	10,586	118,631
	<u>239,228</u>	<u>67,973</u>	<u>307,201</u>
Land .....	87,400	92,817	180,217
	<u>\$326,628</u>	<u>\$160,790</u>	<u>\$487,418</u>

The property located at 693 Sutter Street, San Francisco, is subject to a deed of trust to The Connecticut Mutual Life Insurance Company as collateral for a note with a balance of \$32,014 at June 30, 1969.

## 7. TRUST FUNDS

These funds are summarized as follows:

For Mr. and Mrs. Ben H. Read .....	\$ 63,000
Morris Herzstein Bequest .....	20,196
Life insurance retirement plan for legal counsel .....	51,391
	<u>\$134,587</u>

The portion of the Trust Funds applicable to the retirement or similar benefit to Mr. and Mrs. Ben H. Read, has not been segregated from other assets of the corporation as provided by the bylaws, as such funds are presently invested in United States Treasury securities of indivisible denominations.

The life insurance retirement plan for legal counsel is offset by the cash surrender value of a life insurance policy.

# WOMAN'S AUXILIARY

FORTIETH ANNUAL CONVENTION

MARCH 8 to 11, 1970

Headquarters: San Francisco Hilton Hotel

Convention Chairman: Mrs. Robert F. Gobar

Convention Co-Chairman: Mrs. Norman C. Fox

REGISTRATION: Rosewood Suite, San Francisco Hilton Hotel

Sunday, March 8—9:00 a.m. to 4:00 p.m.

Monday, March 9—8:00 a.m. to 4:00 p.m.

Tuesday, March 10—8:30 a.m. to Noon

SATURDAY, MARCH 7—Pre-Convention

4:00 p.m. — Presentation of Mrs. Edmund Mahon, Auxiliary President, to CMA House of Delegates, Imperial Ballroom. Doctors' wives are invited to attend.

SUNDAY, MARCH 8

9:00 a.m. — Executive Committee Breakfast Meeting, President's Suite

1:30 p.m. — Pre-Convention Board Meeting, Whitney Room

MONDAY, MARCH 9

9:00 a.m. — Opening Session of House of Delegates, Imperial Ballroom

1:30 p.m. — Afternoon Session of House of Delegates, Imperial Ballroom

TUESDAY, MARCH 10

9:00 a.m. — Final Session of House of Delegates, Imperial Ballroom

12:30 p.m. — Presidents' Luncheon and Fashion Show, honoring Mrs. Edmund Mahon, Mrs. Kenneth J. McNiece, Past State Presidents, and CMA Advisory Board and wives, Hilton Plaza

3:00 p.m. — Presentation of Mrs. Kenneth J. McNiece, Incoming Auxiliary President, to the CMA House of Delegates, Imperial Ballroom.

WEDNESDAY, MARCH 11—Post-Convention

8:00 a.m. — Post-Convention Board of Directors Meeting—Mrs. Kenneth J. McNiece, President, presiding, Teakwood Suite

10:00 a.m. — Orientation Meeting — Mrs. Kenneth J. McNiece, President, presiding, Teakwood Suite. 1970-1971 State Board Members, District Councilors, County and District Board Members are welcome.

HOSPITALITY CENTER—Rosewood Suite

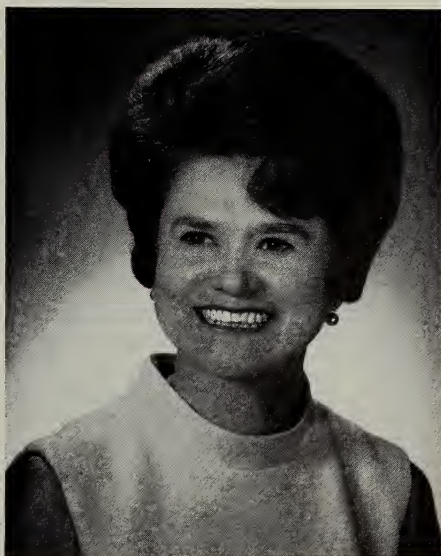
Sunday, March 8 — 9:00 a.m. to 4:00 p.m.

Monday, March 9 — 8:00 a.m. to 4:00 p.m.

Tuesday, March 10 — 8:00 a.m. to 11:00 a.m.



MRS. EDMUND MAHON, *President*



MRS. KENNETH J. MCNIECE  
*President-Elect*

## Technical Exhibits

TECHNICAL EXHIBITS will be housed in the Hilton Hotel's Mezzanine Floor which may be reached from the main floor of the hotel by elevator or escalator. Here the many exhibitors will present their products and services for members of the Association.

All exhibits and all products exhibited have been screened by a committee as a means of eliminating those which do not meet high standards. The exhibitors agree to this procedure and agree that by this means each will be in good company.

Here in one area will be found the latest developments in

drugs, equipment and services to aid the physician in his professional activities. All physicians are urged to visit the exhibits; meetings have been planned to allow ample time for this important activity. Your visit will not only help bring your own knowledge up to date, but also, it will demonstrate to our exhibitors, who contribute so much to the success of the meeting, that we recognize and appreciate their fine cooperation.

Exhibits will be open from 12 noon Saturday to 6 p.m. On Sunday, Monday and Tuesday from 9 a.m. to 5 p.m. and on Wednesday, from 9 a.m. to 12 noon.

**ABBOTT LABORATORIES** Booth 13  
North Chicago, Illinois

**APACHE CORPORATION** Booth 42  
Minneapolis, Minnesota

**ARMOUR-DIAL, INC.** Booths 43 & 44  
Chicago, Illinois

DIAL RESEARCH & DEVELOPMENT CENTER invites you to visit the "golden floor" exhibit. Featuring Dial soap, the unsurpassed skin cleanser that reduces harmful skin bacteria with unsurpassed antibacterial effectiveness. Dial soap's unsurpassed mildness has, also, been proven in clinical tests with infants. And its unsurpassed substantivity means that Dial soap builds an invisible bacteriostatic film on the skin that provides protection against harmful bacteria between washings. And, while you're at the exhibit you can obtain a sample of Dial soap and the clinical data documenting its effectiveness. Dial . . . the unsurpassed skin cleanser.

**ARMOUR PHARMACEUTICAL COMPANY** Booth 102  
Chicago, Illinois

The Armour Medical Sales representatives cordially invite the members of the California Medical Association to visit the ARMOUR PHARMACEUTICAL COMPANY booth. CHYMORAL-100 TABLETS (enzyme tablets) and LETTER TABLETS (sodium levothyroxine, Armour) will be featured. The latest literature and clinical studies will be available.

**ARNAR-STONE LABORATORIES, INC.** Booth 79  
Mount Prospect, Illinois

AMERICAN TOPICAL ANESTHETIC—20 percent dissolved benzocaine in a water-soluble base—ointment, suppositories and aerosol forms. HAZEL-BALM—Cooling, soothing witch hazel and emollient lanolin in aerosol form. ISOCLOR—Oral nasal decongestant and bronchodilator—tablet, liquid and timesule forms, also the anti-tussive ISOCLOR expectorant. SOPOR—Non-barbiturate hypnotic sedative for gentle untroubled sleep. Particularly useful with geriatric patients.

**ASTRA PHARMACEUTICAL PRODUCTS, INC.** Booth 72  
Worcester, Massachusetts

Information and descriptive literature pertaining to XYLOCAINE® (lidocaine) and CITANEST® (prilocaine) local and topical anesthetics, and iron preparations ASTRAFER® (dextriferron) for intravenous use and JECTOFR® (iron sorbitex) for intramuscular administration will be available at the ASTRA booth.

**AUDIO DIGEST (Pacific Medical Equip. Co.)** Booth 49  
Los Angeles, California

**AUTOMATED MANAGEMENT SYSTEMS** Booth 64  
c/o PRODATA CORPORATION  
Santa Rosa, California

**AYERST LABORATORIES** Booth 94  
New York, New York

**BACTI-LAB INC.** Booth 84  
Mountain View, California

URO-BACTI-LAB, a diagnostic product, is presented as a quality, convenient and economical 45 second technique for performing a simultaneous urine culture, colony count, bacterial identification and sensitivity test, all essential in the busy office for the modern diagnosis and treatment of symptomatic or an asymptomatic urinary tract infection. AERCO, an unusual culture incubator with an optional use CO<sub>2</sub> chamber is also presented.

**BANK OF AMERICA — BUSINESS SERVICES** Booth 104  
San Francisco, California

**BERKELEY BIOLOGICALS** Booth 109  
Berkeley, California

**BEVERLY MEDICAL SUPPLY** Booth 107  
Sun Valley, California

**BREON LABORATORIES, INC.** Booth 97  
New York, New York

BREON LABORATORIES INC. presents a full line of products for the care of patients with chronic obstructive pulmonary diseases. Included are ALEVAIRE, BRONKOMETER, BRONKOSOL, BRONKOTABS, BRONKOTABS-HAFS, BRONKOLIXIR and BRONKEPHRINE. Supplying a variety of formulas, dosage forms and actions these products offer both prophylaxis and therapy, in chronic or acute conditions, to all ages. BREON personnel will gladly discuss specific products and therapies with you.

**BRISTOL LABORATORIES** Booth 82  
Syracuse, New York

**BROWN PHARMACEUTICAL CO.** Booth 71  
Los Angeles, California

**BURROUGHS WELLCOME & CO. (U.S.A.) INC.** Booth 5  
Tuckahoe, New York

Of particular interest at this meeting is ZYLOPRIM brand Allopurinol which represents a unique concept for the management of gout, uric acid nephropathy and calculi, and hyperuricemia due to neoplastic disease and/or its intensive treatment. ZYLOPRIM was first synthesized in the WELLCOME RESEARCH LABORATORIES in Tuckahoe, New York in 1956 and is the first drug to be marketed which reduces the formation of uric acid at its source.

**CARNATION COMPANY** Booth 68  
Los Angeles, California

**CARRIAGE COMPANIES** Booth 36  
Fremont, California



- CASS & JOHANSING** Booth 1  
Los Angeles, California  
Representatives will be present to discuss insurance programs for members of the medical profession in California—Guaranteed Renewable Disability; Non-Cancellable Disability; Life; Accidental Death & Dismemberment. In addition, assistance in complete insurance programming will be available.
- CIBA PHARMACEUTICAL COMPANY** Booth 89  
Summit, New Jersey
- COCA COLA CALIFORNIA/NEVADA BOTTLERS ASSOCIATION** Booth 9A  
San Francisco, California  
Sampling COCA-COLA and FRESCA.
- DAYLIN MEDICAL & SURGICAL SUPPLY** Booths 39 & 40  
Los Angeles, California
- DOME LABORATORIES** Booth 68  
West Haven, Connecticut  
You are cordially invited to visit the DOME exhibit and discuss with our trained representatives some of the dermatological preparations we have developed. With hot weather approaching, we particularly invite your attention to UVAL LOTION, a sun screen preparation that has proven to be so effective in preventing sun burn and blistering.
- EMKO COMPANY** Booth 77  
St. Louis, Missouri  
The EMKO COMPANY exhibits the first aerosol foam contraceptive. EMKO VAGINAL CONTRACEPTIVE FOAM has been professionally recommended for over eight years. It has a high level of effectiveness and is substantially free from side effects. Women appreciate the esthetic qualities of EMKO VAGINAL CONTRACEPTIVE FOAM. Literature and samples of EMKO VAGINAL CONTRACEPTIVE FOAM and MY OWN HYGIENE DEODORANT SPRAY and TOWELETTES will be distributed from the EMKO exhibit.
- ENCYCLOPAEDIA BRITANNICA, INC.** Booth 50  
Chicago, Illinois  
ENCYCLOPAEDIA BRITANNICA welcomes delegates to the California Medical Association session. As part of EB's 200th anniversary, we will have on display the great new edition of *Britannica*, *Great Books of the Western World*, the *Britannica Junior*, *EB Replica*, the *Annals of America*, *Compton's Encyclopaedia* etc. Stop and inspect these products in Booth 50. They are available to the delegates at our convention offer.
- CHARLES O. FINLEY & CO., INC.** Booth 69  
Los Angeles, California  
CALIFORNIA MEDICAL ASSOCIATION Disability Insurance Program. Information is available.
- FULLER LABORATORIES, INC.** Booth 75  
Eden Prairie, Minnesota  
"TUCKS Family of Products" TUCKS medicated pads, TUCKS TAKE-ALONGS, TUCKS Witch Hazel Ointment, Cream and Cream HC for management of pruritus ani, hemorrhoidal and perineorrhaphy discomfort. FULLER SHIELD dressing used following anorectal surgery, and its companion, A.R.D. butterfly-shaped anorectal dressing. SCOPETTES—Proctosigmoidoscopic swabs lint-free, holds shape wet or dry.
- GROESBECK, A. J. ASSOCIATES** Booth 66  
Beverly Hills, California
- HARPER & ROW PUBLISHERS INC.** Booth 106  
New York, New York  
Among the new books on hand are Baserga and Malamud: *Autoradiography: Techniques and Application*; Hollinshead: *Anatomy for Surgeons—The Back and Limbs*, 2nd Edition; Kennedy et al: *Textbook of Vectorcardiography*; Peters et al: *The Fine Structure of the Nervous System*; Moertel and Reitemeier: *Advanced Gastrointestinal Cancer*; Cooper: *Involuntary Movement Disorders*; Freeman and Johnson: *Clinical Scintillation Scanning*; and Glenn and Boyce: *Urologic Surgery*.
- JANRUS RECORDERS CORP.** Booth 73  
Beverly Hills, California  
You are cordially invited to visit the JANRUS RECORDERS CORP. booth where our representatives will be happy to demonstrate and answer any questions regarding their full line of cassette tape recorders and dictating equipment designed for office, home, meetings, travel, and car. We feature the following brands of recorders: CONCORD, UHER, PANASONIC, AMPEX, CROWN, NORELCO, AIWA, SHARP.
- KEY PHARMACEUTICALS** Booth 87  
Miami, Florida
- LEDERLE LABORATORIES** Booth 108  
Pearl River, New York  
LEDERLE LABORATORIES is pleased to support the 1970 Annual Session of the California Medical Association by its presence at this meeting. Our trained representatives in Booth 108 will be glad to discuss our well-known brand name drugs such as DECELOMYCIN®, the world's foremost broad-spectrum antibiotic, PATHIBAMATE®, FILIBON®, FERRO-SEQUELS®, and our other products applicable to your practice. Information is also available on our many other services to medicine.
- LILLY, ELI & CO.** Booth 12  
Indianapolis, Indiana
- LOMA LINDA FOODS** Booth 105  
Riverside, California  
LOMA LINDA FOODS, one of America's oldest manufacturers of fiber-free, hypoallergenic infant soy milk, will show evidence of the nutritional adequacy of the product SOYALAC. Representatives will explain why it is unusual in that it does not settle out, is milk-like in texture, and does not tend to raise infants' serum cholesterol. Uses for adult patients and in cholesterol-lowering diets will be discussed. Samples will be served and recipes presented indicating the versatility of the product in diets of those with milk allergies or who for other reasons need to eliminate dairy milk from the diet.
- MARION LABORATORIES** Booth 91  
Kansas City, Missouri
- MEAD JOHNSON LABORATORIES** Booth 83  
Evansville, Indiana  
The MEAD JOHNSON LABORATORIES' exhibit has been arranged to give you the optimum in quick service and product information. To make your visit productive, specially trained representatives will be on duty to tell you about their products.
- MEDICAL MANAGEMENT CONTROL** Booth 80  
San Francisco, California  
Seattle, Washington  
Management consultants to the medical profession specializing in: Group Practice Management, Professional Incorpora-

- tion, Partnership Formation and Operation, Office Management, Systems and Procedures, Taxes and Tax Planning, Net Worth Growth Projection, Organization and Development of Professional Facilities. Member: Society of Professional Business Consultants, Association of Management Consultants, American Management Association.
- MERCK SHARP & DOHME** Booth 9  
West Point, Pennsylvania  
The MERCK SHARP & DOHME exhibit has been designed to offer a contribution to your therapeutic armamentarium. Technically trained personnel are available to discuss the scope and variety of services offered to physicians.
- MISSION PHARMACAL COMPANY** Booth 62  
San Antonio, Texas  
MISSION PHARMACAL COMPANY will be featuring the following products:  
FOSFREE®—A superb calcium supplement. IROMIN-G®—A hematinic with vitamins for the patient who does not tolerate oral iron. PRULET®—a non-systemic prune-like laxative. FETAMIN®—For appetite control. EQUILET®—The patients' first choice in antacid therapy. HOMAPIN® LIQUITAB®—The first pediatric antispasmodic in a flavored chewable dosage form. MISSION PRENATAL™—A well tolerated prenatal hematinic.
- NETTLESHIP COMPANY OF LOS ANGELES** Booth 85  
Los Angeles, California  
Administrators of Professional Liability, Group Income Protection, and Life Insurance Programs for County Medical Associations and Trusts in California. Qualified representatives available to discuss problems pertaining to hospital or individual professional liability coverage, income protection, life or other types of insurance. Literature which will assist in the prevention of claims and various forms to be used to protect, as far as possible, against malpractice claims.
- NIAGARA THERAPY MFG. CORP.** Booth 110  
San Francisco, California  
NIAGARA CYCLO-MASSAGE—massaging equipment, portable and furniture for home and professional use.
- ORTHO PHARMACEUTICAL CORPORATION** Booth 67  
Raritan, New Jersey
- PARKE, DAVIS & COMPANY** Booth 4  
Detroit, Michigan  
PARKE-DAVIS welcomes your visit to our booth and the opportunity to discuss with you a group of our most important pharmaceutical specialties. Included in this year's exhibit are FLUOGEN®, PAREST®, and NORLESTRIN Fe®. Our full line of support hosiery will also be shown. Please feel free to stop and discuss these PARKE-DAVIS products with the medical service representatives attending our exhibit.
- PASADENA RESEARCH LABS, INC.** Booth 86  
Pasadena, California
- PERSON & COVEY** Booth 57  
Glendale, California
- PFIZER LABORATORIES DIVISION** Booth 10  
New York, New York
- RITTER CO. DIV. SYBRON** Booth 103  
Rochester, New York
- SANDOZ PHARMACEUTICALS** Booth 90  
Hanover, New Jersey  
SANDOZ PHARMACEUTICALS cordially invites you to visit our display at Booth 90, where we are featuring MELLARIL, HYDERGINE, SANSERT, CAFERGOT P-B, FIORINAL and BELLERGAL. Any of our representatives in attendance will gladly answer questions about these and other SANDOZ products.
- SAN JOSE SURGICAL SUPPLY, INC.** Booth 46  
San Jose, California
- W. B. SAUNDERS COMPANY** Booth 98  
Philadelphia, Pennsylvania  
SAUNDERS will have on display a complete line of their medical books, including many new titles and new editions—such as, DeLand and Wagner: *Nuclear Medicine*; Leeds and Taveras: *Angiography*; Bondy: *Duncan's Diseases of Metabolism*; Hinshaw: *Diseases of the Chest*; Conn: *1970 Current Therapy*; Scheie and Albert: *Adler's Textbook of Ophthalmology*; Flint: *Emergency Treatment*; Lynch and Raphael: *Laboratory Technology*; and many others.
- SCHERING LABORATORIES** Booth 65  
Union, New Jersey  
SCHERING LABORATORIES invites you to visit their exhibit, Booth 65, where their representatives will be available to discuss with you any questions you may have on VALISONE®, ETAFON®, GARAMYCIN®, CELESTONE®, SOLUSPAN® Injection, DRIXORAL®, TINACTIN®, AFRIN®, or any other SCHERING product.
- SCHOLL MANUFACTURING CO.** Booth 100  
Chicago, Illinois
- G. D. SEARLE & CO.** Booth 8  
Chicago, Illinois  
You are cordially invited to visit the SEARLE booth where our representatives will be happy to answer any questions regarding Searle Products of Research. Featured will be information on OVULEN-21, OVULEN-28, ENOVID, ALDACTAZIDE, FLAGYL, LOMOTIL, PRO-BANTHINE and other drugs of interest.
- SIERRA MEDICAL SALES** Booth 60  
Riverside, California  
DIAPULSE therapy provides safe and effective treatment through stimulation of normal body defenses. DIAPULSE is of particular value in increasing peripheral blood flow and accelerating wound healing.
- SMITH KLINE AND FRENCH LABORATORIES** Booth 99  
Philadelphia, Pennsylvania  
Representatives will be on hand to answer your specific questions and provide information on their products and services.
- SMITH, MILLER & PATCH, INC.** Booth 78  
New York, New York  
SMITH, MILLER & PATCH, INC. will feature our new non-barbiturate hypnotic, SOMNAPAC and SOMNAPAC FORTTE; DECONAMINE, a potent oral antihistamine and decongestant in three dosage forms; PYOCIDIN HC Otic Solution; VASOCIDIN Ophthalmic-Otic Solution; our hematinics, VITRON-C and VITRON-C PLUS; and our specialty bowel regulator, KON-DREMUL.
- SPACELABS, INC.** Booth 63  
Chatsworth, California  
The SPACELABS exhibit will display the most recent developments and products for coronary and intensive care and surgical monitoring. Display will feature ECG Telemetry, Bed-side Monitors, Central Station Monitors, and a wide variety of Physiological Preamplifiers.

SPECTRUM FINANCIAL GROUP Beverly Hills, California	Booth 74	SYNTEX LABORATORIES, INC. Palo Alto, California	Booth 48
SQUIBB, E. R. & SONS, INC. New York, New York	Booth 7	SYNALAR® (fluocinolone acetonide), the topical cortico-steroid designed to meet specific dermatologic needs, will be featured at Booth 48. SYNALAR has set a new standard of success in the treatment of a wide range of inflammatory dermatoses. A warm invitation is extended to all physicians attending this meeting to visit our booth and discuss the latest developments from SYNTEX research.	
STACEY'S OF SAN FRANCISCO, INC. Palo Alto, California A Subsidiary of Bro-Dart Industries Medical books are displayed.	Booth 14	UPJOHN CO., THE Kalamazoo, Michigan	Booths 95 & 96
STUART DIV./ATLAS CHEMICAL INDUSTRIES, INC. Pasadena, California	Booth 6	WARNER CHILCOTT LABORATORIES Morris Plains, New Jersey	Booth 101
SURGICAL MECHANICAL RESEARCH, INC. Newport Beach, California	Booth 3	WARREN TEED PHARMACEUTICALS, INC. Columbus, Ohio	Booth 17
SYNTEX LABORATORIES, INC. Stanford Industrial Park, Palo Alto, California Visit Booth 70 for prescribing information on NORINYL® 1+80, now available in convenient 21-and 28-day oral contraceptive regimens and packaged in the feminine, convenient and attractive MEMORETTE® dispenser.	Booth 70	WYETH LABORATORIES Philadelphia, Pennsylvania	Booth 11
<div style="border: 1px solid black; padding: 10px;"> <p style="text-align: center;"><b>SYNTEX SPECIAL TOUR</b></p> <p>Ask our representative about the luncheon and seminar tour of our plant at Palo Alto, on Tuesday, March 10, 1970.</p> </div>		<p>WYETH will feature OVRAL®, each tablet contains 0.5 mg norgestrel with 0.05 mg ethinyl estradiol, Wyeth. SERAX®, (oxazepam) Wyeth, capsules. Full information is available at Booth 11.</p>	



# *application for* **HOTEL ACCOMMODATIONS** **NINETY-NINTH *Annual Session***

**CALIFORNIA MEDICAL ASSOCIATION • MARCH 7-11, 1970**

**SAN FRANCISCO HILTON HOTEL, SAN FRANCISCO**

**HOUSE OF DELEGATES OPENING SESSION, HILTON HOTEL, SATURDAY EVENING, MARCH 7;  
SCIENTIFIC SESSIONS, HILTON HOTEL, BEGIN SATURDAY NOON, MARCH 7**

1. Fill in the form below *completely* for room accommodations at the CMA's 1970 Annual Session. There are only a limited number of rooms available. Your choice of accommodations will be better if your request is for rooms to be occupied by two or more persons.
2. Your reservation request should include the definite date and hour of your arrival and departure.
3. All reservations must be made through the CMA Housing Bureau, Suite 260, Fox Plaza, San Francisco, California 94102, by February 6, 1970.
4. **CANCELLATIONS:** Please notify CMA Housing Bureau, Suite 260, Fox Plaza, San Francisco 94102 of all cancellations up to 15 days before Annual Session. Within last 15 days, make cancellations directly with hotel.  
**CHANGES:** All other changes to be made directly with hotel at all times. Rooms will not be held after 6 P.M. unless a later arrival time has been requested. Failure to notify the hotel of any change in your arrival time may result in cancellation of your reservation.

	Single	Double or Twin	Suites
<b>SAN FRANCISCO HILTON</b> ..... Mason & O'Farrell	\$19-29	\$25-38	\$65 and up
<b>ST. FRANCIS</b> ..... Powell & Geary	19-33	24-38	55-123
<b>SIR FRANCIS DRAKE</b> ..... Powell & Sutter	17-25	21-30	75
<b>CLIFT HOTEL</b> ..... Geary & Taylor	none	25-35	none
<b>HANDLERY INN</b> ..... 260 O'Farrell	none	27-30	none
<b>CHANCELLOR HOTEL</b> ..... 433 Powell	none	15-18	none
<b>MARK HOPKINS</b> ..... California & Mason	24-38	31-45	55-160

SEND TO: California Medical Association Housing Bureau  
Suite 260, Fox Plaza, San Francisco, California 94102

Please reserve the following accommodations for the CMA's 1970 Annual Session in San Francisco, March 7-11.

Single Bedroom \$ ..... Twin-Bedded \$ ..... Double Bed \$ ..... Suite \$ .....  
First Choice Hotel ..... Second ..... Third .....  
Arrival (date) ..... Hour ..... a.m. p.m. Departure (date) ..... Hour ..... a.m. p.m.

THE NAME AND ADDRESS OF EACH HOTEL GUEST MUST BE LISTED. Include names and addresses of *each* person in a double or twin-bedded room, and names and addresses of *all other persons* for whom you are requesting reservations.

Your Name: ..... Officer? .... Delegate? .... Alternate? .... Speaker? ....  
Address: ..... County .....  
City and State ..... Zip Code .....

GUESTS' NAMES AND ADDRESSES:

.....  
.....  
.....

# they need the proved effectiveness and safety of **K-LYTE**®

Each effervescent tablet supplies: 2.5 Gm. potassium bicarbonate (25 mEq. elemental potassium), 2.1 Gm. citric acid, cyclamic acid

Three clinical studies\* confirm the effectiveness of good tasting K-Lyte as a source of supplemental potassium to increase low levels of serum potassium and to maintain normal levels. Patients were on continuous diuretic therapy and salt-restricted diets. K-Lyte dosage was one tablet b.i.d.

## Serum Potassium Levels (in mEq./L)

Number of patients	Mean initial value	Mean final value
14	3.23	4.83
16	3.50	4.40
25	4.52	4.47

K-Lyte can offer effective potassium supplementation without the gastrointestinal complications sometimes associated with potassium chloride tablets and thiazide-potassium chloride combination therapy. Effervescent K-Lyte is taken in solution, speeding up absorption to avoid these hazards.

**Composition:** Each tablet contains potassium bicarbonate (2.5 Gm.), citric acid (2.1 Gm.), cyclamic acid, artificial flavor and color.

**Contraindications:** When renal function is impaired, or if the patient has Addison's disease, potassium supplementation should not ordinarily be instituted.

**Precautions:** Should not be used in patients with low urinary output unless under the supervision of a physician. In established hypokalemia, attention should be directed toward correction of frequently associated hypochloremic alkalosis and other potential electrolyte disturbances. Patients should be directed to dissolve tablet in stated amount of water to assure against gastrointestinal injury associated with the oral ingestion of concentrated potassium salt preparations.

**Side Effects:** While nausea has been reported in an occasional patient, K-Lyte produces no serious side effects when given in recommended doses to patients with normal renal function and urinary output. Potassium intoxication causes listlessness, mental confusion, tingling of the extremities and other symptoms associated with a high concentration of potassium in the serum.

**Administration and Dosage:** K-Lyte effervescent tablets must be dissolved in 3 to 4 ounces of water before taking. Adults: 1 tablet 2 to 4 times daily, depending on the requirements of the patient. Two tablets (50 mEq. of elemental potassium) supply the approximate normal adult daily requirement.

**How Supplied:** Effervescent tablets—boxes of 30 and 250 (orange or lime).

\*Reports on file: Medical Research Department, Mead Johnson Laboratories, Evansville, Indiana 47721

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71770

**Mead Johnson**  
LABORATORIES

### PHYSICIANS WANTED

**PHYSICIANS FOR LIFE INSURANCE EXAMINATIONS**—all areas of Southern California. Contact: Edward B. Frankel, M.D., 5203 Lakewood Boulevard, Lakewood, California 90712. Phone: (213) 531-7420.

**WANTED**—Three Internists. One General Practitioner for growing eight man multi-specialty group at foot of Sierras. Close to outdoor recreation. 2½ hours from Los Angeles. Start \$5,000 plus. Partnership—9 months. John Bugay, Drummond Medical Group, 1111 North China Lake Blvd., Ridgecrest, Calif. 93555. Phone collect (714) 446-4571.

**DIRECTOR OF PUBLIC HEALTH**, \$1775-\$1975 per mo. Responsible for formulation and administration of comprehensive Public Health program. Requires graduation from recognized medical school and possession of or eligibility to obtain California Medical License. Some experience in administrative capacity in a Health Dept. or graduate study in school of public health is desirable. Apply: Civil Service Commission, County Govt. Center, Madera, Calif.

**WANTED**—Pathologist for well established medical-laboratory group in Los Angeles county. Excellent salary plus fringe benefits and percentage. Available now to those with California license. Write: Rancho Park Station, P.O. Box 64338, Los Angeles, Calif. 90064.

### SITUATIONS WANTED

**OPHTHALMOLOGIST**—Board certified—desires to relocate to Southern California. Nine years in practice—seeking association with group or individual. Box 9203, California Medicine.

### OFFICES FOR LEASE, RENT OR SALE

**ATTENTION PEDIATRICIANS**—Medical suite available, 600 sq. ft., reasonable rent. Internists, generalists, OB, Gyn and clinical laboratories now renting. Dr. I. N. Tucker, 25 Evergreen Avenue, Mill Valley, Calif. 388-5164.

**SAN FRANCISCO, CALIFORNIA**—Excellent prestigious Sutter Street location in completely refurbished six story Medical Building with outstanding medical tenants. Rent or lease at very reasonable rates. Several suites with up to 1100 square feet available now. Reply: Draper Financial Corporation, Russ Building, San Francisco, Calif. 94104, (415) 989-5600.

**ANAHEIM, CALIFORNIA**—New Spanish architecture medical building adjacent to 150 bed West Anaheim Community Hospital—South of Knotts Berry Farm on Beach Boulevard. Suites 900 to 1250 square foot. Contact Administrator's Office, West Anaheim Community Hospital, 3053 West Orange Avenue, Anaheim, Calif.

### PRACTICES WANTED

**CALIFORNIA MEDICAL practices wanted.** Licensed broker specializing in sale of medical practices. We handle advertising and all negotiations. For information contact nearest office Professional Practice Sales, 17411 Irvine Blvd., Tustin, Calif., (714) 832-0230, or 1428 Irving St., San Francisco, Calif., (415) 661-0608. All inquiries strictly confidential.

### FOR RENT

**HAWAIIAN (HANEI, KAUAI)** Vacation beach home for only \$500 per month. Old Hawaiian atmosphere, away from crowded beaches. Excellent skin diving, swimming and beaches. Weekly rate \$150.00. For details, pictures and information write Box 9194, California Medicine.

### PRACTICES FOR SALE

**GENERAL PRACTICES** for sale as follows: San Clemente, Anaheim, Garden Grove, Los Angeles (4), Lynwood, Lakewood, Venice, Riverside, San Francisco (2), Hayward, Lake Tahoe, Santa Maria, etc. Also, large Southern Calif. industrial practice grossing \$250,000. OB-GYN practice, San Mateo; Internal Medicine (3); Orthopedic practice, San Fernando Valley. Cash office practice downtown L.A. grossing \$15,000 monthly. Other general and specialty practices coming up. For placement on free mailing list contact Professional Practice Sales. Southern Calif. office at 17411 Irvine Blvd., Tustin (714) 832-0230; Northern Calif. office at 1428 Irving St., San Francisco, Calif. (415) 661-0608.

**SOUTHERN CALIFORNIA** — Fantastic general practice. Gross \$100,000. Easy. Assume by March 1, 1970. Leaving State. Box 9201, California Medicine.

**SANTA BARBARA**—Busy, well established women's-children's practice for sale due to retirement. Above average gross. Will introduce. In air conditioned Medical Center Building, well located. Reply: Helen Hart, M.D., 1919 State Street, Santa Barbara, Ca. 93101.

### EQUIPMENT WANTED

**MEDICAL LABORATORY group** wishes to buy Medical Laboratories or X-ray facilities in Los Angeles or Orange Counties with large gross. All replies confidential and will be acknowledged. Write: Rancho Park Station, P.O. Box 64338, Los Angeles, Calif. 90064.

### ASSOCIATES WANTED

**YOUNG GENERAL PRACTITIONER**—A.A.G.P. to associate with two active M.D.'s (One F.A.C.S.), strictly general practice, in desirable coastal town with population area of 25,000; excellent opportunity. Hospital soon to be built, open staff policy. Well-equipped offices, pro-rated expenses. Box No. 845, California Medicine.

### FOR SALE

**ARE YOU A KEEN YACHTSMAN?**  
**ISLAND STRIDER**, 35 ft. GRP sloop, designed by Kim Holman for ocean racing, built in England in 1968 with special modifications for cruising in the Caribbean, is available for bare boat charter out of Grenada. Complete inventory for 4, including linen and cutlery, 80 watt R/T set, inflatable dinghy and outboard. Details from: "Island Strider," c/o Grenada Yacht Services, P.O. Box 183, St. George's, Grenada, West Indies.

### References and Reviews

**LSD in Treatment of Alcoholism** — F. G. Johnson (477 Waterloo St., London, Ontario), Amer. J. Psychiat. 126:481-487 (Oct.) 1969.

A single-blind study of 95 alcoholic patients was carried out in order to determine the efficacy of LSD treatment. Four treatment groups were maintained: LSD was given with and without a therapist present, sodium amobarbital-methamphetamine hydrochloride was given with a therapist present, and the fourth group underwent routine clinic care. At one-year follow-up, with 87 percent of the patients reporting, all four groups showed significant improvement in employment and drinking, but there was no significant difference between the groups on any one criterion measure. This study does not support the claims made for the efficacy of LSD treatment of alcoholism.

**Serologic Responses of Children After Primary Vaccination and Revaccination Against Smallpox**—H. Wulff, T. D. Y. Chin, and H. A. Wenner (National Communicable Disease Center, Kansas City, Kan.), Amer. J. Epidem. 90:312-318 (Oct.) 1969.

Three serologic test methods were used to study immunologic responses of 36 children vaccinated against smallpox. Following successful primary vaccination, 97 percent of the children converted for neutralizing and HI antibodies and 19 percent for CE antibodies. During the 15-month interval between primary vaccination and revaccination, three of 33 children had a fourfold or greater decrease for neutralizing antibodies, but 29 of 33 children had a decrease for HI antibodies. All children became negative for CE antibodies. After the second vaccination 15 months later in which

(Continued on page 42)





## **KINESED®**

- With belladonna alkaloids—for the hyperactive and spastic bowel
- With phenobarbital—for associated anxiety and tension
- With simethicone—for accompanying gas discomfort

### **Composition**

Each chewable, fruit-flavored, scored tablet contains: 16 mg. phenobarbital (warning: may be habit-forming); 0.1 mg. hyoscyamine sulfate; 0.02 mg. atropine sulfate; 0.007 mg. scopolamine hydrobromide; 40 mg. simethicone.

### **Contraindications**

Hypersensitivity to barbiturates or belladonna alkaloids, glaucoma, advanced renal or hepatic disease.

### **Precautions**

Administer with caution to patients with incipient glaucoma, bladder neck obstruction. Prolonged use of barbiturates may be habit-forming.

### **Side effects**

Blurred vision, dry mouth, dysuria, and other atropine-like side effects may occur at high doses, but are only rarely noted at recommended dosages.

### **Dosage**

Adults: One or two tablets three or four times daily. Dosage can be adjusted depending on diagnosis and severity of symptoms. Children 2 to 12 years: One half or one tablet three or four times daily. Tablets may be chewed or swallowed with liquids.

**Stuart**

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only one child failed to respond clinically, 78 percent of the children had a fourfold or greater neutralizing antibody rise; in contrast, only 18 percent showed a significant HI antibody titer increase; 44 percent converted for CF antibodies.

**Serum FSH and LH Measurements in Evaluation of Menstrual Disorders**—W. J. Dignam, A. F. Parlow, and T. A. Daane (Harbor General Hosp., Torrance, Calif.), *Amer. J. Obstet. Gynec.* 105:679-695 (Nov. 1) 1969.

Presented data indicate that a number of disorders of the menstrual cycle are compatible with follicle stimulating hormone (FSH) and luteinizing hormone (LH) levels within the range of normal as determined by radioimmunoassay methods. Assay of a single randomly selected serum specimen for FSH and LH in subjects with such disorders would not permit differentiation from women with normal menstrual cycles. The characteristic which most clearly differentiates amenorrheic women from those with normal cycles is the lack of the typical midcycle hypersecretion of LH and FSH ordinarily present in women.

**Surgical Treatment of Vertigo**—J. L. Pulec (2122 W. Third St., Los Angeles), *Laryngoscope* 79:1783-1822 (Oct.) 1969.

Vertigo-producing conditions that are amenable to surgical treatment generally involve the acoustic nerve or vestibular labyrinth. Four types of surgical procedure can be employed. Shunt operations may be performed to equalize the pressures of the otic and periotic systems for the relief of Ménière's disease. Middle fossa vestibular nerve section may be performed. Destructive labyrinthectomy or VIIIth nerve section and removal of cerebellopontine angle tumors may be used. Two hundred and eighty-three operations were performed on 236 patients. The relief afforded these patients has been most encouraging.

**Etiology and Management of Severely Burned Children**—J. C. Holter and S. B. Friedman (Univ. of Rochester Medical Center, Rochester, N.Y.), *Amer. J. Dis. Child.* 118:680-686 (Nov.) 1969.

Optimal overall management of the severely burned child and his family demands consideration of the psychologic and social factors that may have made the child vulnerable to this type of injury. These factors are examined in 13 burned children, and in ten cases gross emotional disturbances within the families appeared to have propelled the children into situations resulting in severe burns. The cases reported illustrate that most childhood burns may be categorized as reflecting a true accident, a situational crisis, or child abuse (battered child syndrome).

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## Special Article

# Etiologic Diagnosis of Lower Respiratory Tract Infections

PAUL D. HOEPRICH, M.D., *Davis*

■ *Decision as to the role of infection in lower respiratory tract disease requires examination by culture of specimens known to be derived from the infra-laryngeal respiratory tract. Methods that involve the upper respiratory tract in collection of specimens entail the hazard of contamination by microbiota resident in the upper respiratory tract.*

*The extrapulmonary approaches of cutting-needle biopsy and needle aspiration of intrathoracic disease have not been impressively productive of etiologic diagnosis of infections. While open-chest surgical biopsy has been a highly effective means to diagnosis, this approach does have special requirements in facilities and technical skills.*

*Percutaneous transtracheal aspiration of tracheo-broncho-pulmonary secretions-exudates has been productive of useful information. Because of inherent simplicity and safety, transtracheal aspiration should precede resort to more demanding, difficult, dangerous procedures.*

PHYSICIANS ARE OFTEN called upon to solve the problem of lower respiratory tract disease. Assessment of the role of infection is obligatory and is

frequently difficult. Consider the patient who has low grade fever, mild leukocytosis, radiographic evidence of pulmonary disease, and cough productive of mucopurulent sputum that yields no potentially pathogenic bacteria on culture. Or, the patient with chronic, obstructive, pulmonary disease who feels unwell, reports increased production of sputum, but does not have either fever or leukocytosis — yet *Staphylococcus aureus*, *He-*

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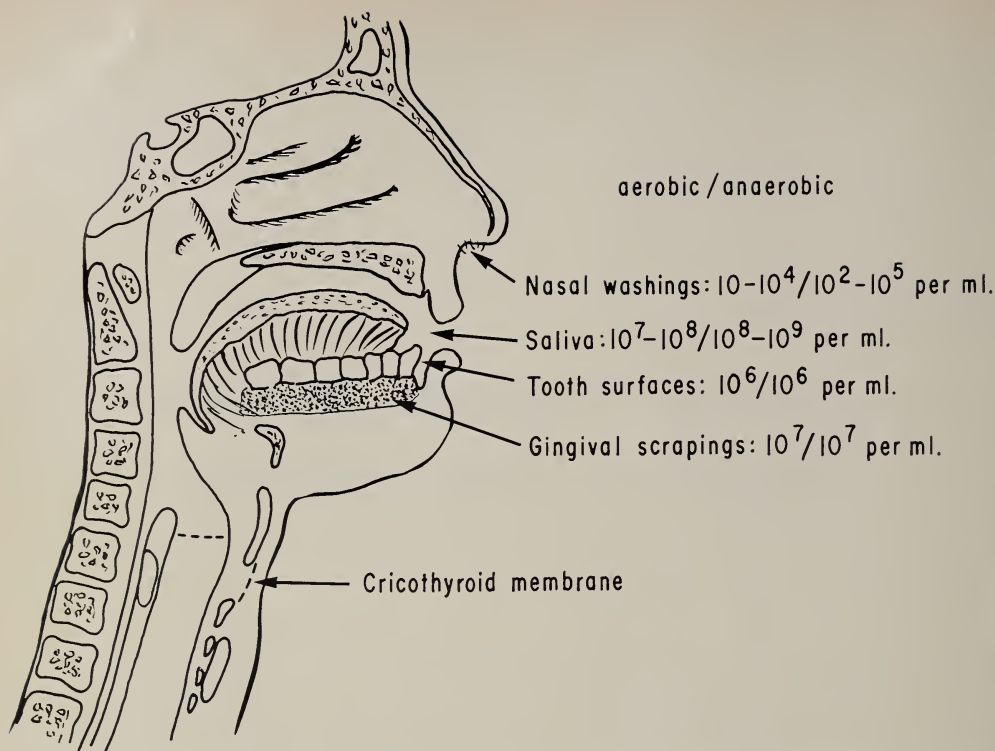


Figure 1.—The supra-laryngeal respiratory tract abounds with microorganisms. Quantitative data, presented above, are available with regard to bacteria and fungi.<sup>1</sup>

*mophilus influenzae*, *Escherichia coli* and *Neisseria catarrhalis* are isolated from the sputum.

Accurate etiologic diagnosis is quite essential in cases such as these, for infectious agents are likely to be involved. But even the primary judgment as to the presence or absence of infection is rendered difficult by the anatomical and ecological facts of the matter. The passage of exudate (as sputum) from the areas of affliction (the lung; bronchi; trachea) through regions of remarkably high density in microbial population (the pharynx, mouth) virtually assures some growth on culture. The need is to secure specimens of lower respiratory tract exudates that can be certified to be free of contamination with microbiota resident in the supra-laryngeal respiratory tract. The rationale, technique and safety of various methods advocated to fill this need are considered in this paper, with emphasis on potential for diagnostic yield of infectious agents.

There are two approaches to securing secretions-exudates that are truly representative of the lower respiratory tract—that portion of the respiratory tract that lies below the larynx. These are: (1) via the upper respiratory tract; (2) through extra-respiratory structures.

### Upper Respiratory Tract Approaches

The hazard common to every method for getting at the lower via the upper respiratory tract is contamination by microorganisms from the nasal-oral-pharyngeal regions. Considering only bacteria, the numbers normally available in the nasal and oral regions are truly astounding (Figure 1). *Staphylococcus* sp. predominate in the nose,<sup>1</sup> whereas the oral flora consists primarily of streptococci (*viridans* group; anaerobic) and non-pathogenic *Neisseria* sp. With poor oral hygiene and dental prostheses Gram-negative bacilli are common. When antimicrobial agents have been

applied, Gram-negative bacilli, *Staphylococcus aureus*, *Candida albicans* may predominate.

While the pharynx is the crossroads of the respiratory and alimentary tracts, in lymphoid endowment and in epithelial covering it is much more akin to the gut. Nevertheless, *viridans* group streptococci and nonpathogenic *Neisseria* sp. predominate in the normal pharynx, as in the normal mouth. In addition, certain potentially pathogenic bacteria are so frequently found in the oropharynx of normal persons that they, too, must be considered part of the normal bacterial flora: *Staphylococcus aureus*; *Streptococcus pyogenes*, Group A; *Diplococcus pneumoniae*; *Hemophilus influenzae*.<sup>1,2</sup> Again, the usual impact of treatment with antimicrobial agents is quantitative dominance by Gram-negative bacilli, *S. aureus*, *C. albicans*.

Expectoration

Expectoration of sputum provides multiple opportunities for the addition of microbiota resident in the upper respiratory tract to the specimen. Washing the sputum was suggested many years ago as a way to minimize such contamination.<sup>3,4,5</sup> Two modern studies verify the effectiveness of washing expectorated sputum:

1. Upper respiratory tract contamination was signalled by growth of *Serratia marcescens* in cultures of sputum following swab application of a broth culture of this bacterium to various oral and pharyngeal sites before collection of expectorated sputum. Nine washings, each with an equal volume of sterile saline solution, were required to remove *S. marcescens* garnered from pharyngeal sites; three washings sufficed when the contaminant was picked up from oral areas.<sup>6</sup>

2. Serial, three-fold washing of a selected, choice, small quantity of purulent, expectorated sputum in 10 to 15 ml portions of sterile saline solution, after the fashion of Mulder *et al*,<sup>5</sup> was judged by Lapinski and co-workers<sup>7</sup> to be quite effective in removing contaminating microorganisms.

Although effective, washing sputum is tedious and has not gained general acceptance. Moreover, washing can give no clue as to the actual origin of the sputum that was expectorated and then washed—for example, “sputum” may originate from the paranasal sinuses.

TABLE 1.—As Applied in Bronchoscopy, Both Lidocaine and Tetracaine are Inhibitory to Microorganisms in Tracheo-Broncho-Pulmonary Secretions.<sup>11,12</sup>

Microorganisms	Cultures Positive			
	Lidocaine		Tetracaine	
	With/ Without	Percent Inhibited	With/ Without	Percent Inhibited
Fungi:				
<i>Candida</i> sp.	1/?	?	0/?	?
Bacteria:				
Non-acid-fast	33/33	0	16/40	60
<i>Mycobacterium tuberculosis</i>	13/19	31.6	16/20	70

Tracheal Suction

“Tracheal” suction implies passage of a catheter, by way of either the nose or mouth, into the trachea in order to aspirate sputum. It is supposed that gross contamination from the upper respiratory tract will be avoided in this way, and also that the lower respiratory tract origin of the specimen will be indubitable. However, two drawbacks seriously hamper this approach. First, reflex exclusion of foreign objects from supralaryngeal entry into the trachea is so vigorous that the battle is not always successful in the conscious, unanesthetized patient; a common outcome is aspiration of oropharyngeal “sputum.”

Second, if passage through the larynx into the trachea is achieved, it follows after passage of the catheter through regions teeming with resident microbiota; hence invariably the catheter used to collect the specimen is contaminated.

Bronchoscopy

Bronchoscopy entails tracheal contamination with oral and pharyngeal secretions as the instrument is passed through the anesthetized upper respiratory passages into the lower respiratory tract. For this reason, material aspirated through the bronchoscope is quite frequently seeded with potentially pathogenic microorganisms that originate in the upper respiratory tract.<sup>8,9</sup> Use of extraordinary apparatus in conjunction with bronchoscopy apparently will minimize contamination.<sup>6</sup> However, as bronchoscopy is ordinarily carried out, supplementation of qualitative culture with a quantitative technique is probably a more practical route to distinguishing contamination from actual lower respiratory tract infection.<sup>10</sup>

Beyond the factor of instrument-borne contamination, there is another, unique hazard to valid culture when the specimen is collected at bronchoscopy. The local anesthetics that must be applied

TABLE 2.—Summary of Several Reports of Cutting-Needle Lung Biopsy.<sup>17-23</sup>

Author(s) [Year]	No. of Patients Infected/Total	No. of Specimens		Complications		
		Cultured	Dx of Infection	Pneumothorax*	Bleeding	Other†
Sabour <i>et al</i> [1960]	8/164	?	0	1	1	5
Miller [1960]	0/10	?	0	2	1	0
Manfredi <i>et al</i> [1963]	1/16	16	1	2(1)	0	0
Aronovitch <i>et al</i> [1963]	0/48	?	0	6	0	2
Smith [1964]	0/61	?	0	25	6	4
Krumholz <i>et al</i> [1966]	17/126	126	1	12(6)	2	0
Adamson <i>et al</i> [1967]	2/62	?	0	12(5)	3	1(1)
Totals	28/487	142	2	60(12)	13	12(1)

\*Number of patients requiring suction therapy.

†Number of deaths.

to permit bronchoscopy inhibit the growth of non-acid-fast and acid-fast bacteria, as well as fungi.<sup>11,12,13</sup> Of lidocaine and tetracaine, the two agents most commonly employed in bronchoscopy, lidocaine is of lesser antimicrobial potency (Table 1). With both agents, the intensity of the antibiotic effect is directly related to both duration and intensity of exposure. That is, culture of specimens obtained at bronchoscopy are most likely to yield valid results when a minimal quantity of lidocaine is used for local anesthesia, and the specimen is inoculated as soon as possible after collection.

### Extra-Pulmonary Approaches

Contamination by the microbiota normally resident in the upper respiratory tract can be avoided by entering the lower respiratory tract via extra-respiratory approaches. To this can be added certainty of region of origin of the specimen and reliability of culture results—based on the knowledge that during life, the infra-laryngeal respiratory tract is normally sterile.<sup>6,9,14-16</sup>

### Biopsy

Two techniques of obtaining biopsy specimens from lower respiratory tract lesions will be considered: cutting needle excision and open chest surgical excision. Ordinarily, neither technique is employed with the sole or primary aim of securing material for culture. Indeed, failure of etiologic diagnosis of lower respiratory tract infectious diseases is the usual outcome with cutting needle biopsy. Needle biopsy specimens from 16 patients were cultured by Manfredi and coworkers; all were sterile, although one patient had tuberculosis.<sup>17</sup> Krumholz and coworkers<sup>18</sup> cultured tissue fragments and washings of needle biopsy specimens from 126 patients, detecting

*Nocardia asteroides* one time—the sole etiologic diagnosis by culture among the 17 patients judged, by other means, to have lower respiratory tract infections (11 tuberculosis—2 miliary, 3 histoplasmosis, 2 coccidioidomycosis). Pooling these data, one of 18 (5.6 percent) infections in the lower respiratory tract were specifically diagnosed by culture of needle biopsy specimens. Moreover, complications are frequent—see the summary of the data of several reports of cutting needle lung biopsy in Table 2. Pneumothorax occurred in 60 of 487 (12.3 percent) patients, requiring treatment in 12 patients. Bleeding was induced in 13 (2.7 percent) patients and was usually manifest as hemoptysis—12 patients. However, cutting needle biopsy was diagnostic in 370 of the 487 patients (76.0 percent). Diffuse, noninfectious pulmonary disease, and neoplasia were the processes most readily diagnosed.

Open chest excision of biopsy material permits the surgeon to select grossly diseased lower respiratory tract tissues, as well as parietal pleura and vicinal lymph nodes. Such specimens are generally adequate in size and are quite reliable for culture. In this connection, it cannot be emphasized too strongly that a portion of each biopsy specimen must be submitted for culture (non-acid-fast, acid-fast, anaerobic, fungal) at the time of biopsy. When this is done, as has been urged by Gaensler and coworkers,<sup>24</sup> etiologic diagnosis of infectious processes is usual. The inclusion of presently available methods for culture of *Mycoplasma* sp. and viral agents may possibly clarify diagnoses such as non-specific chronic pneumonitis. There is hazard to open chest surgical biopsy. As summarized in the report of Gaensler *et al*, there were seven deaths among 441 patients (1.6 percent); complications exceeded 59 (>13.4 percent) with pneumothorax and subcutaneous emphysema the commonest events.



## Aspiration

Aspiration techniques have been applied in the diagnosis of intra-thoracic disease via percutaneous insertion of a needle through the chest wall at least since 1883.<sup>25</sup> At first, aspiration was employed to obtain exudate from pneumonic consolidations so that rapid, unimpeachable bacteriologic diagnosis could be made. The ascendancy of serotherapy, in obliging specific etiologic diagnosis, made for the widest application of the method. Revival of the technique was recently suggested,<sup>26</sup> because of: (1) the obligation for intelligent selection from the variety of specifically active antimicrobial therapeutic agents now available; (2) the burgeoning resistance in microorganisms to some of these agents; (3) the frequency of pneumonic infection in persons with compromised body defenses. Since these are valid arguments for rapid, specific, etiologic diagnosis of any infectious process, it is the adequacy of percutaneous aspiration of the lung (transthoracic lung puncture) as a means to etiologic diagnosis of pneumonias that must be judged. As reviewed by Gherman and Simon,<sup>26</sup> from 17 percent to 90 percent of aspirates of pneumonias will yield growth of microorganisms. Both false positive (2 of 18 or 11.1 percent) and false negative (5 of 18 or 27.8 percent) results occur.<sup>26</sup> Pneumothorax, the commonest complication, ranged in frequency from 1 percent to 22 percent.

Although aspiration was introduced as a means to etiologic diagnosis of pneumonia, after radiographic examination of the chest became common, discrete pulmonary lesions were aspirated. In a recent report,<sup>27</sup> with visualization using biplane image amplification, lesions as small as 1 cm in diameter were impaled by a needle inserted percutaneously into the chest. Maintenance of negative pressure while juggling the needle tip within lesions allows aspiration of material for examination. Such use of aspiration has been of greatest value to diagnosis of intrathoracic neoplastic lesions: 754 aspirations in 641 patients resulted in detecting malignant change in 309.<sup>27-29</sup> Examination of aspirates by culture was not always carried out. Indeed, the reported data<sup>27-29</sup> are so sparse in this regard that it is difficult to evaluate the utility of aspiration in diagnosis of discrete intra-thoracic infections. Complications seem to follow aspiration about as frequently as cutting-needle biopsy—12.2 percent and 17.5 percent, respectively (Table 6).

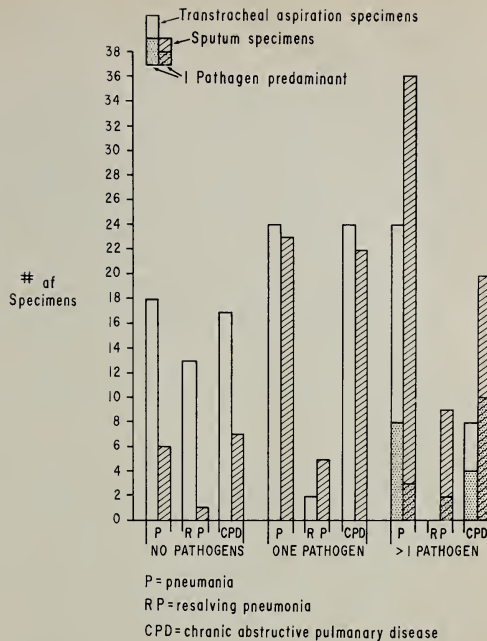


Chart 1.—The yield of potentially pathogenic bacteria and fungi is displayed as a function of the underlying lower respiratory tract disease. The results with 129 simultaneously acquired and identically studied transtracheal aspirate and sputum specimens are contrasted.

Percutaneous entry into the trachea provides yet another route of access to the lower respiratory tract that bypasses the upper respiratory tract. Transtracheal puncture through the cricothyroid membrane was introduced in 1922<sup>30</sup> to facilitate injection of iodized poppy seed oil into the tracheobronchial tree preparatory to bronchography. Induction of tracheal anesthesia for bronchoscopy<sup>31</sup> and endotracheal intubation<sup>32</sup> are modern applications of the transtracheal injection technique.

In 1959, Pecora reported on aspiration of tracheo-broncho-pulmonary secretions-exudates through a small, plastic catheter passed into the trachea via a needle inserted through the cricothyroid membrane.<sup>33</sup> Our original report<sup>16</sup> validated the utility of transtracheal aspiration in diagnosis of lower respiratory tract disease. This study has been extended by one of us\* through identical

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examination of 58 additional, paired transtracheal aspiration and sputum specimens (17 acute pneumonia; six resolving pneumonia; 35 chronic obstructive pulmonary disease) obtained from 56 patients. As before, there was no mortality and there were no additional instances of morbidity. Specifically, infection of the needle track did not occur. The augmented data are presented in Chart 1. Again, the disparity between transtracheal and sputum specimens was most pronounced with regard to absence of potentially pathogenic microorganisms, and presence of more than one potential pathogen. Absence of potential pathogens occurred in 48 of the aspirate and 14 of the sputum specimens from the total of 129 paired specimens considered in Chart 1. At the other extreme, 32 of the aspirate and 65 of the sputum specimens yielded more than one potential pathogen. The excess of potentially pathogenic microorganisms found in sputums were mostly Gram-negative bacilli and *Staphylococcus aureus* (see Table 3).

The relevance of these culture findings to the actual respiratory diseases of the patients who yielded the specimens is attested by:

TABLE 3.—Potential Pathogens Isolated From Sputums, But Not From Corresponding Transtracheal Aspiration Specimens

Isolates	Pneumonia (65 Cases)	Chronic Obstructive Pulmonary Disease (49 Cases)
Gram-negative bacilli	16	15
<i>Staphylococcus aureus</i>	10	2
<i>Diplococcus pneumoniae</i>	4	5
<i>Hemophilus influenzae</i>	1	2
<i>Candida albicans</i>	2	2

- The fact of improvement in clinical status in 43 patients in whom antimicrobial therapy was either stopped (23 patients) or altered (20 patients) according to the cultures of the transtracheal aspirate specimens.

- The necropsy findings in five patients who died within 24 hours after transtracheal aspiration (Table 4).

Our studies support transtracheal aspiration as useful in excluding upper respiratory tract contaminants and providing valid information about lower respiratory tract infections. In two studies by other investigators transtracheal aspiration was compared with other techniques for specimen acquisition.<sup>7,8</sup> The data presented in Table 5 also support the concept that transtracheal aspiration provides specimens of secretions-exudates that are truly representative of tracheo-broncho-pulmonary diseases.

The record of transtracheal aspiration continues to be good in that complications are minor so long as the precautions previously recommended are observed.<sup>16</sup> Entry of air into the tissues is minimized by: (1) the rapidity with which the procedure is ordinarily carried out—the catheter lying threaded through the skin into the trachea for less than a minute; (2) proper selection of patients. The procedure should not be applied in patients who have: (1) any impairment of blood clotting; (2) severe, intractable cough; (3) indicated unwillingness to remain at rest in bed for 8 to 12 hours after the procedure.

Transtracheal aspiration is not a routine procedure to be employed in every patient with pneu-

TABLE 4.—Data on Five Patients Who Died of Their Underlying Disease Within 24 Hours After Transtracheal Aspiration and Were Also Examined Postmortem

Age	Sex	Clinical Impression	Results of Transtracheal Aspiration	Post-mortem findings and cultures
76	M	Aspiration pneumonia	Large no. of <i>Pseudomonas aeruginosa</i> ; Large no. of <i>Streptococcus pyogenes</i> (Group A)	Extensive bronchopneumonia, <i>P. aeruginosa</i> , <i>S. pyogenes</i> (Group A), alpha-hemolytic streptococci and tellurite-positive <i>Staph.</i> species grown from bronchi
65	F	Probable pulmonary infarction	No growth	Massive pulmonary embolism with infarction, recent; no broncho-pulmonary cultures obtained
75	M	Bilateral bacterial bronchopneumonia	Large no. of <i>C. albicans</i>	Bilateral bronchopneumonia; <i>C. albicans</i> grown from lung
65	M	Pneumonia, possibly viral	No growth	Extensive resolving pneumonia, with hyaline-membrane formation; no growth of bacteria, fungi or pleuropneumonia-like organisms.
68	M	Pneumonia complicating a cerebrovascular accident	Large no. of <i>Enterobacter aerogenes</i> ; Large no. of <i>Staphylococcus aureus</i>	Acute tracheo-bronchitis; <i>Enterobacter aerogenes</i> ; <i>Staphylococcus aureus</i>

TABLE 5.—Sputum Washing Was Compared With Transtracheal Aspiration: 14 Specimens by Lapinski et al<sup>7</sup> and 71 Specimens by Miklos<sup>8</sup>

Isolate	Washed Sputum		Transtracheal Aspiration	
	Lapinski	Miklos	Lapinski	Miklos
None	0/14 = 0%	4/288 = 1%	2/14 = 14%	24/71 = 34%
Non-pathogens	0/14 = 0%	175/288 = 61%	0/14 = 0%	0/71 = 0%
<i>Hemophilus influenzae</i>	5/14 = 36%	3/288 = 1%	5/14 = 36%	5/71 = 7%
<i>Diplococcus pneumoniae</i>	10/14 = 72%	10/288 = 3%	8/14 = 57%	5/71 = 7%
<i>Staphylococcus aureus</i>	0/14 = 0%	10/288 = 3%	0/14 = 0%	6/71 = 8%
Coliforms	0/14 = 0%	30/288 = 10%	0/14 = 0%	9/71 = 13%
<i>Pseudomonas aeruginosa</i>	1/14 = 7%	3/288 = 1%	1/14 = 7%	0/71 = 0%

TABLE 6.—Comparison of Various Methods for Securing Specimens of Lower Respiratory Tract Secretions/Exudates

Method (references)	No. of Procedures	Years of Studies	Mortality	Morbidity	Potential Pathogens
Washed sputum <sup>7,8</sup>	408	1964-1967	0	0	217 (53.2%)
Bronchoscopy <sup>9,34-38</sup>	530	1943-1958	0	0	395 (74.5%)
Biopsy:					
Cutting needle <sup>17-23</sup>	487	1960-1967	1 (0.2%)	84 (17.3%)	Infrequent
Open chest <sup>18</sup>	441	1949-1964	7 (1.6%)	>59 (>13.4%)	Infrequent
Aspiration:					
Diffuse disease <sup>26</sup>	2,189	1911-1965	?	?	912 (~41.6%)
Localized lesions <sup>27-29</sup>	754	1939-1967	3 (0.4%)	89 (4.8%)	<50 (<6.6%)
Transtracheal <sup>7,8,16,33</sup>	305	1963-1968	0	1 (0.3%)	173 (56.7%)

monia. It is of value when there is: (1) no clear predominance of one potential pathogen in the sputum; (2) doubt as to the validity of a predominant potential pathogen in cultures of sputum; (3) failure of production of sputum; (4) poor response to antimicrobial therapy; (5) concern that superinfection may have intervened in the lower respiratory tract.

As a means for etiologic diagnosis of lower respiratory tract infections, transtracheal aspiration compares favorably with other techniques (Table 6). Also, transtracheal aspiration is a bedside procedure, and serious complications are quite uncommon.

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## ONCOLOGY FELLOWSHIPS

Clinical Research Fellowships in Oncology and Cancer Chemotherapy are now available at the University of Southern California School of Medicine. The fellowships are of one or two years' duration and will begin 1 July 1970 and 1971, or at another date by special arrangement.

The Oncology Service comprises 37 beds, plus an outpatient clinic with 40 to 50 visits weekly. Fellows have broad patient responsibility and supervise four residents. Both standard and investigational chemotherapy is carried out under the supervision of Dr. Joseph Bateman, chairman of the Western Cooperative Cancer Chemotherapy Group. An active hematology, cytogenetics and biochemistry laboratory is an integral part of the Service.

The first year can include a three month rotation on the Hematology Service of Los Angeles County-USC Medical Center. The optional second year can include a three month rotation on the Radiation Therapy Service, or it may be devoted to a laboratory project.

The stipend for the first year is \$9,300 to \$10,000, of which \$3,600 is tax-free, and additional allowance is made for advanced status.

A year of fellowship can substitute for a year of residency for board eligibility. Applicants should have completed at least one year of medical residency and be eligible for a California license, but need not be U.S. citizens.

They should send a brief resume to David C. Stolinsky, M.D., USC Oncology Service, John Wesley Hospital, 2825 South Hope Street, Los Angeles, California 90007.

# A Controlled Study of L-DOPA In Parkinson's Disease

W. W. HOFMANN, M.D., AND R. L. RYAN, M.D., *Palo Alto*

■ *A small group of patients with Parkinson's disease were treated with oral L-DOPA. In ten cases the drug was given according to a randomized, double-blind-crossover protocol, and in 13 cases both the physician and the patient knew what treatment was being given. With subjective bias at a minimum the salutary effects of the amino acid were confirmed in 90 percent of the patients. The general level of improvement with L-DOPA was better than with standard agents, and a combination of drugs was sometimes very helpful.*

*Toxic psychosis was a problem in three cases, but other adverse reactions were minimal.*

*Further extensive trial and study is indicated.*

ALTHOUGH A NUMBER of reasonably effective agents are commercially available for the treatment of Parkinson's disease, it is a common clinical experience that many patients suffer gradual progression of their symptoms and become resistant to one, and then to most, drugs. The physician then tries to substitute one compound for another, usually without much hope of real success because of the fact that almost all standard drugs depend for their action on a common atropine-like property. What is the result of drug resistance and what is from an actual increase in the number of diseased neurons is not always clear in a given instance, but in either case the disability may worsen in parallel with increasing drug requirements until, in many cases, bothersome or toxic side effects of treatment appear.

A further complication with present treatment methods is drug-induced drowsiness or lethargy which may seriously interfere with the patient's overall work performance and may leave him quite depressed.

The clinician who must treat many patients with Parkinson's disease can hardly escape the feeling that current drug therapy is at best purely symptomatic and that nothing is really being accomplished in slowing or reversing the nerve cell-death within the brain.

The pioneering experiments of Birkmayer and Hornykiewicz,<sup>1</sup> Barbeau<sup>2</sup> and Cotzias<sup>3</sup> with L-DOPA have opened a new therapeutic avenue in this chronic disabling disease, and, for the first time, the treatment constitutes a form of direct metabolic support or replenishment of a vital process in some of the affected nerve cells. The amino acid is an immediate precursor of the catecholamine, dopamine, whose concentration has been found to be significantly reduced in the brains of patients dying with Parkinson's disease. The present theory is

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that dopamine-containing neurones connecting the substantia nigra with globus pallidus and putamen are somehow depleted of their neurotransmitter by the disease process and that disturbances of muscle tone, posture, and tremor appear because of imbalances between the action of this "monoaminergic" system and other motor outflows which are presumably cholinergic. Hornykiewicz<sup>4</sup> published an excellent review of the subject in 1966.

As with clinical trials of any new drug, however, there is the problem of objective data interpretation, and the literature indicates that some observers are not fully convinced of the value of the amino acid. To take two examples, Fehling<sup>5</sup> has said, on the basis of a double blind study, that DOPA is completely ineffective, and Greer and Williams<sup>6</sup> have arrived at the same conclusion. We present here a short study of a few patients in which we believe we have reduced subjective bias to a satisfactory level by the use of a double blind technique, and the encouraging results we wish to report suggest that previous criticisms may have arisen largely because of errors in experimental design.

## Material and Methods

We treated ten patients with advanced Parkinson's disease in a six-week inpatient drug study using L-DOPA and have given the drug to seven of these and to an additional 13 as outpatients. The total number of patients to be reported is 23. During the hospital course the patients were treated for two 21-day periods with gradually increasing doses of either lactose or L-DOPA according to a randomized, coded program prepared in the hospital pharmacy. After signing the informed consent, each patient was aware that he would be given a placebo for one-half of the study. At the end of the first treatment period the patient was given a one to five day "rest" and then started on a second course of identical-appearing capsules, the content of which was again unknown to the patient or to the physician. Considering the short half life of both lactose and L-DOPA, the variability of the washout period was not important in the overall response.

During the last ten days of each treatment period the patients were receiving a fixed dose of eight capsules (4 grams) per day. Seriously disabled patients were sometimes continued on their regular medications (two out of ten), but the usual procedure was to withdraw standard drugs and

thus to permit the patient's signs and symptoms maximum expression during the several days required to complete baseline studies. A comprehensive disability rating scale was made out for each patient, and the daily rating estimates were made after the drug was started. The general scale provided for four to ten degrees of disability in several categories, including walking, dressing, eating, self-care, speech, postural stability, tremor, rigidity, and finger dexterity.

If a patient was clearly worsening at a rapid rate in one or the other treatment phase at a time when the total daily dose of drug was still less than the 4 grams per day maximum, an attempt was made to carry on to completion of that treatment period by adding small amounts of standard drugs. The alternative was to list the patient as a failure in that treatment phase and switch immediately to the drug supply for the second three-week course. If worsening continued, the code was broken, the patient was given full doses of his original medication, and the double blind portion of the study was terminated. The patient was then given an opportunity to enroll in the chronic, or outpatient phase, a study to last at least an additional year.

Patients were selected for inclusion in the double blind study if they were mentally competent, could give reliable reports, and were severely disabled with rigidity or akinesia or both. The age range was from 48 to 76 years.

Of the original ten patients in the acute phase, seven were enrolled in the chronic group reported here. These seven are the only ones in the long-term outpatient portion who may be considered "controlled." The remaining 13 in the outpatient phase were evaluated purely on the basis of disability rating scales and questionnaires. Patients having mainly tremor were not included, though two patients whose previous tremor had been relieved surgically were treated. The laboratory investigations included complete blood count including erythrocyte sedimentation rate (ESR) and urinalysis, fasting blood glucose, two-hour postprandial glucose, a Coombs test, blood urea nitrogen, bleeding and clotting time, skull and chest x-ray films, electrocardiogram and any other relevant studies in all the 23 patients reported here, whether they were in the blind-controlled study or not. Many of the tests were repeated at weekly intervals. Serial electroencephalograms were also obtained at weekly intervals throughout both treatment periods. After the treatment code was broken



for any patient the EEG's and other laboratory data accumulated during the placebo phase were used as control and were compared with results in the period on L-DOPA.

Each patient was asked to make a guess as to whether he had received an effective drug during a given three-week treatment period, and these statements were later correlated with the actual drug data from the pharmacy. The results in the ten hospitalized patients on L-DOPA were also compared with those from two patients previously treated in the hospital on a double blind basis with DL-DOPA, up to 10 grams per day.

Patients with drug-induced rigidity or tremor were not admitted to the study, and no patient was given reserpine or any similar drug during DOPA treatment. Three of the patients were so disabled as to require wheelchairs at the time of admission, and all had undergone extensive trials on various standard drugs. When physical therapy treatments had been of help to the patients before they received DOPA, these treatments were continued during the stay in hospital. Patients with previous myocardial infarction were not excluded, but if there was a history or clinical evidence of a focal cerebrovascular lesion within the preceding five years, the patient was not enrolled. All patients had been diagnosed as having Parkinson's disease for at least several years before the study. Follow-up examinations and evaluations were at weekly intervals for about four visits, then monthly.

## Results

The most obvious finding in these experiments was that, despite every effort to quantify the known disabilities of the disease before and after treatment, the patients' initial responses were seldom measurable on any of the many numerical scales applied during the acute, inpatient phase. Thus, both the placebo control and long-term drug administration were essential in assessing the real value of L-DOPA. The lengthy records of how much time was required for various activities of daily living, as well as the daily numerical assessment of everything from speech to posture, appeared to be of no real value in the six-week experiments in the hospital, and even those changes that could be measured were not useful in predicting later responses in the outpatient part of the study. This is not to say that no objective changes were recorded in the double blind phase, as a few patients made measurable improvements

and others clearly worsened on all scales—the latter during the placebo administration only in all but one patient. The latter patient (No. 6, Table 1) who deteriorated on DOPA during the short inpatient phase of the study later showed progress and substantial benefit during long term outpatient treatment.

The second major finding was that, even those patients who had shown no improvement at all on the inpatient phase of the study, might begin to show favorable responses after two to three months treatment at a slightly higher daily dose. Moreover, some patients who showed no response for two months or more might then begin to improve and show a slight but definite improvement for a further three- to five-month period. No patient followed has shown any deterioration of his condition while on L-DOPA. Of the 20 followed for an average of five to eight months (range three to ten months), three are on standard drugs and for two DOPA has been discontinued. The first patient in whom DOPA was discontinued was terminal and had shown only minimal response, the second showed a possible toxic reaction and minimal improvement.

Since numerical rating changes were usually not available in the first phase of the study, it was necessary to make some crude estimate of drug and placebo effects in the double blind portion, and for this purpose the responses were evaluated in accord with answers to the following questions:

1. If there was a definite worsening in one treatment period, did the agent of the other period prevent the decline?
2. If there was worsening in one treatment period, did the other drug actually reverse it?
3. Whether there was temporary worsening in one phase or not, did the patient experience some relief of symptoms in one treatment period?
4. Did the patient feel better while receiving placebo?

When the answer to any of questions 1 through 3 was yes but to question 4 was no, then the L-DOPA was judged to have had a beneficial therapeutic effect. Such responses were obtained in eight patients, and three were listed as failures. The first failure was the patient described above, and there was in addition a patient who indicated improvement on placebo but not on active drug (No. 9, Table 1). The latter response was also considered a failure and the patient was not enrolled in the chronic phase. The third failure was

TABLE 1.—Data on Medication at Beginning of Study Period and Switches from It to DOPA and Placebo

Pt. No.	Condition on Entry	Standard Drugs	Rx Period I*	Rx Period II*	Rx Period II†	Placebo Given	Subjective Response to Placebo	Interrupted in Acute Phase	Dose (L-DOPA) (grams/day)
1	4	Disc.	Def. worse	Slightly worse	Def. better	Per I	Worse	+	5
2	5	—½	Def. worse	Better	Much better	Per I	Worse	++	5
3	4	Disc.	Worse	No change	Better	Per I	Worse	+	5
4	3	Disc.	Better	Worse	Worse	Per II	Worse	+	5
5	4	Disc.	Much worse	No change	Better	Per I	Worse	+	5
6	4	Disc.	Worse	Much worse	Worse	Per II	Worse	— (L-DOPA)	5
7	4	Cont.	No change	No change	No change	Per I	No change	— (L-DOPA)	5
8	4	Disc.	Better	Worse	Much worse	Per II	Worse	+ (L-DOPA)	5
9	2	Disc.	No change	No change	No change	Per II	Says better	— (L-DOPA)	5
10	3	Disc.	No change	Better	Better	Per I	No change	+ (L-DOPA)	5

\*As compared with condition at time of entry.

†As compared with Rx period II.

Disc. = discontinued.

Cont. = continued.

—½ = reduced by half.

	Admission	Placebo	DOPA	Comparative Effects vs. Placebo	Effects vs. Std. Rx	Percent Patients Improved
TABLE 2.—Numerical Disability Rating for In-Patient Portion of Study: Zero=No Defect —5=Maximum Defect						
Bradykinesia	2.5	3	2	+33%	+25%	75
Plastic rigidity	3	4	2	+50%	+33%	50
Gait disturbance	2	3.5	2	+23%	0	70
Speech impairment	3	4	2	+50%	+33%	80
Postural abnormality	2	2	1.5	+25%	+25%	30
Sialorrhea	2	2	2	0	0	0
Dysphagia	2	3	1	66	50	50
Defect in self care	2	3	1	66	50	60
Feeding	2	3	1	66	50	80

a patient (No. 7) who showed no change in any portion of the study.

The crudity of such scales is obvious, but when numerical data are not yet available, this form of separation permits at least the identification of those placebo responses which would invalidate subjective reports, and the improvement in but one half of the study eliminates nonspecific medication responses. Further, since regular medications were usually withdrawn, it was possible to record the degree of benefit the patient had obtained from standard drugs before entry into the study and to see both the rate of onset of DOPA effects and its relative therapeutic efficacy. We have thus judged L-DOPA to be a useful drug if it maintains the patient at or better than the level achieved by his standard drugs, that is, if it prevents or reverses worsening when regular drugs have been discontinued and a placebo given. If, as in the experiments reported by other investigators,<sup>7,8</sup> the patient had been left on his standard medications, the only valid criterion of DOPA efficacy would be measurable improvement in some portion of the patient's disability, but in our studies we have been able to sample the preventive aspects of DOPA treatment and to compare it with placebo. We have also compared the L-form with DL-DOPA in an addi-

tional two cases and have found the levo form much more effective.

Table 1 illustrates the coarse assessment of the patients who were admitted for the controlled, short-term study, and Table 2 gives, for comparison, an averaged pre- and post-DOPA numerical rating in several of the various rating scales where changes were observed. In Table 3 are listed representative disability levels and responses in a few subjects during the inpatient phase of the study and the abstracts of their replies on a standard questionnaire filled out one to two months after discharge, during which period they knew they were receiving L-DOPA in the doses shown. Table 4 is a summary of the findings in the outpatient phase, including the seven patients who showed benefit on DOPA as inpatients.

## Discussion

We have only a small group of patients in both portions of this study, but we believe the evidence for a beneficial DOPA effect is reasonably clear. Our findings thus confirm those of previous investigators.<sup>7,8,9,10,11</sup> This is not to raise false hopes in treatment of a severe and chronic neurological disorder, but we think the results are sufficiently encouraging to warrant pursuing the treatment

TABLE 3.—Summary of Excellent Results in Four Patients

Patient	Major Disability on Entry	Numerical Classification on Entry Scale 1-5	Numerical Change at End 3 Weeks L-DOPA	Quotes from Patients at 2-6 Months Follow-up
A.	Bradykinesia	3	2	Painting fence, mows lawn, thinking about going back to work. Walks well. Feels "still improving." (On ½ orig. meds.)
	Gait	4	2	
	Speech, swallowing	3	2	
	Rigidity	4	2	
B.	Finger dexterity	3	2	Plays tennis again. Has also resumed shooting hand gun in competition. Can speak well enough to have house guests and entertain. Feels more "alert."
	Speech	3	3	
	Rigidity	3	2	
	Mobility	3	3	
C.	Bedfast (rigid)	4	2	Ambulatory, works about house. Full self help. Family says "miracle." On no other drugs.
	Could not walk	4	3	
	Could not care for self	5	3	
D.	Immobility (wheel chair)	4	2	Can now get out of car or chair. Speech is "less monotonous." Feels "more alive." On no other drugs.
	Sialorrhea	3	1	
	Stiffness	4	2	
	Speech	3	2	

TABLE 4.—Long-term Evaluation of Results of DOPA Treatment in 20 Patients

Patient	DOPA Dosage (grams/day)	Other Drugs	Age	Tremor	Improvement in Symptoms			Mood	Side Effects	DOPA Treatment
					Rigidity	Gait				
1	5	Artane	76	+	+	+	±	Nausea		Continued
2	5	....	63	+	+	+	±	Chorea-dystonia		Continued
3	6	....	67	±	±	±	±	Inapprpr. ADH secretion		Discontinued
4	5	....	58	0	0	0	0	Dystonia—hallucinations		Discontinued
5	5	....	73	++	++	++	++	Dystonia, faintness, hallucinations		Continued
6	5	....	67	±	±	±	±	None		Continued
7	4	....	58	++	++	++	+	None		Continued
8	6	Kemadrin	64	+++	+++	+++	+	Dystonia		Continued
9	8	....	49	No tremor	++	++	±	None		Continued
10	6	Artane	66	+	+	±	+	None		Continued
11	6	....	70	No tremor	+	++	++	Faintness		Continued
12	6	....	50	No tremor	+++	++	++	Chorea		Continued
13	6	....	49	+++	+++	++	++	None		Continued
14	5	....	52	±	+	±	+	None		Continued
15	3	....	78	+	++	++	+++	Anorexia		Continued
16	6	....	60	No tremor	++	+	++	None		Continued
17	6	....	62	No tremor	±	±	±	None		Continued
18	4	....	74	+++	+++	±	+++	Nausea		Continued
19	7	....	67	+++	+++	+++	+	Weakness		Continued
20	7	....	66	0	0	±	++	Dizziness		Continued

Summary of Results: No improvement, 3; slight improvement, 5; moderate improvement, 4; marked improvement, 8.

further. In view of the time required for improvement in many of our patients, it seems possible that the negative reports in some earlier studies simply indicate either inadequate dosage or inadequate length of follow-up. In particular, it appears that a double blind experiment in which DOPA is administered intravenously for a few minutes cannot be expected to give reliable data. As can be seen from the present results, a given patient may show at first no response to DOPA other than to remain as well as he was on his regular medication after that has been withdrawn. Or he may simply return to his pre-hospital stage with DOPA when this is given after a period of gross worsening on placebo.

In longer follow-up, the same patients have shown more definite amelioration of symptoms in all but one case, and, sometimes, they have been able to reduce or eliminate their usual drugs. Here it is worth emphasizing that we removed standard "anticholinergic" therapy whenever possible, not because we are suggesting another unilateral pharmacological approach, but because we wanted to see pure DOPA effects. In fact, it may be appropriate, in light of current views on the pathophysiology of Parkinson's disease,<sup>12,13</sup> to aim in most cases for a program of combined therapy, particularly where tremor is a major complaint.

Transient hallucinations appeared in three pa-



tients at the beginning of DOPA therapy, and these same patients later had minor choreic movements of neck and face, the latter not severe enough to require interruption of treatment. Three others complained of dose-dependent nausea, and in two patients there was transient weakness and dizziness, but no significant laboratory abnormalities have developed in any patient on L-DOPA in the dose range from 4 to 6 grams per day. As in previous investigations the psychological effects and nausea could be reduced or eliminated by reducing the dose of DOPA, and it was possible to continue the drug by adding small amounts of standard medication. A very useful side effect in most of the patients studied so far is a feeling of well-being or alertness, and it may be this subjective response that enables the patient to try more activities. When effective doses of DOPA are used the patient thus presents quite a different picture from the person who becomes drowsy on standard medication, and that fraction of the DOPA response that arises from mood elevation is a welcome addition to the therapeutic armamentarium.<sup>13</sup>

Considering all the subjective and objective changes that one can observe in the patient with Parkinson's disease on L-DOPA treatment, we think that the compound deserves more extensive clinical trial. In our study the amino acid has shown a wider spectrum of therapeutic effects than is usually seen with any one of the standard drugs.

#### TRADE NAME AND GENERIC NAME

L-DOPA® . . . . . 3,4-L  $\beta$ -(dihydroxyphenylalanine)

#### ACKNOWLEDGEMENTS

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#### SMOKE GETS IN YOUR EYES

"If a patient comes to you complaining of burning eyes, ask whether he is a smoker. In my experience, smoking a pack of cigarettes a day is one of the commonest causes of red lids and burny eyes.

"Something else to consider in the patient with red burning eyes is tranquilizers. It's well recognized now that many of the tranquilizers, particularly the phenothiazines and most frequently Sparine®, depress tear secretion. So many people are taking these things today that you now have to ask everyone what he has in his medicine cupboard."

—MAX FINE, M.D., San Francisco

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# Mediastinoscopy Under Local Anesthesia

## A Valuable Diagnostic Technique

PAUL H. WARD, M.D., *Los Angeles*

■ *Mediastinoscopy is an important, new endoscopic diagnostic technique. The simplicity of the technique and low morbidity and mortality associated with the procedure when carried out under local anesthesia suggest that in many instances mediastinoscopy for direct visualization and excision of biopsy specimens may replace diagnostic thoracotomy in many cases.*

LESIONS OF THE mediastinum and thorax are often difficult diagnostic problems requiring exploratory thoracotomy in order to obtain a tissue diagnosis. The introduction of mediastinoscopy by Carlens, in 1951<sup>1</sup> provided a promising, new simple and safe procedure for exploration, palpation and direct vision removal of biopsy specimens from lesions of the superior mediastinum.

The objectives of this paper are to describe the surgical technique, indications, and complications and, in particular, emphasize the superiority and advantages of performing the procedure under local anesthesia. Representative cases in which mediastinoscopy has been of value are presented and included is a brief discussion on who should perform mediastinoscopy.

Originally the procedure was used to determine the operability of bronchogenic carcinoma without resort to thoracotomy. Experience has shown that it often can be helpful in the diagnosis of other diseases involving the mediastinum. Diseases diagnosed by mediastinoscopy included metastatic

tumors from other areas of the body, tuberculosis, histoplasmosis, sarcoidosis, mediastinal cysts, thymoma, Hodgkin's disease, lymphosarcoma, and other lymphomata, liposarcoma, lipoma, silicosis and vascular anomalies.<sup>2-5</sup> Recently we even removed a foreign body by this technique.

There has been slow acceptance of the procedure in this country, which may be due in part to a lack of familiarity with the anatomy of this area. Pearson<sup>6</sup> believed the term *mediastinoscopy* may suggest to some surgeons "rather formidable and frightening possibilities and may conjure up visions of blind instrumental probing in among the great vessels and vital structures of the mediastinum." Another detracting factor has been the belief that general anesthesia is required.<sup>1-5</sup> Introduction of the technique of performing the mediastinoscopy under local anesthesia<sup>7,8</sup> has increased the simplicity and safety of the procedure. Local anesthesia not only eliminates the hazards of general anesthesia but decreases bleeding, thereby providing better visualization of the mediastinal structures. It shortens the operating room time and allows the surgeon to detect and correct any complications immediately. The results of performing mediastinoscopy under local anesthesia have been so superior that general anesthesia was used in only six of our last one hundred cases.

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## Surgical Technique

It is essential that mediastinoscopy be performed in a general operating room with meticulous sterile technique. Mediastinoscopy is a sterile procedure and should not be considered comparable to other endoscopic procedures which are not sterile, but rather surgically clean procedures. While complications are rare the possibility is always present of injury to the great vessels and pneumothorax, which can be more efficiently managed in the general operating room.

The patient is placed supine on the operating table with the shoulders elevated by a shoulder roll or sand bag. This extends the neck while leaving the head in the midline free to be turned to either right or left. The neck, chin, and upper thorax are prepared and draped in the fashion required for tracheotomy or thyroidectomy. When the procedure is performed under local anesthesia, the skin and suprasternal notch area are infiltrated with 1 percent xylocaine with adrenalin solution. In patients with hypertension or heart disease, the sympathomimetic drug is omitted. A transverse incision 3 to 4 cm long is made in a skin crease about 2 cm above the manubrium. Midline dissection is carried down to the ventral surface of the trachea. Especially important is the division of the pretracheal fascia, since the plane of dissection is against the trachea posterior to this fascia. Failure to delineate the tracheal rings may result in dissection in an incorrect plane and the likelihood of injury to the great vessels.

Approximately 2 ml of 1 percent xylocaine is injected into the lumen of the trachea to diminish the cough reflex. The index finger is used to perform a major portion of the dissection. It gently dissects down the anterior surface of the trachea. It is usually possible to palpate the tracheobronchial angles and carina. Should the patient experience discomfort, several milliliters of 1 percent xylocaine is placed in the wound and massaged into the mediastinal tissues. An evaluation of the upper mediastinum can be made with the palpating finger. The aortic arch, innominate artery and left common carotid artery are easily identified. Any enlarged paratracheal lymph nodes or tumor infiltrates in the mediastinum or against the mediastinal pleural walls can be palpated and their adherence and mobility ascertained. Bleeding, especially when the procedure is performed under local anesthetic, is negligible up to this point.

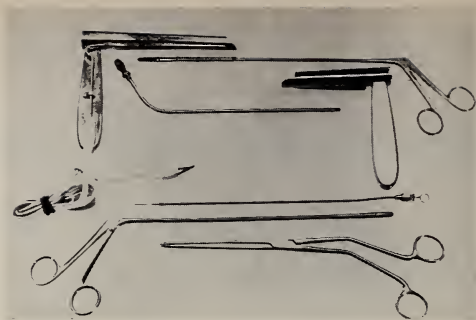


Figure 1.—Special instruments used in the performance of mediastinoscopy include mediastinoscopes, light carriers, suction tubes, cup biopsy forceps, laryngeal scissors, dissector instrument (spreader) and long aspirating needle.

The instruments required for mediastinoscopy include knife, hemostats, small retractors and a few specially designed scopes, scissors, long aspirating needle, biopsy and dissecting forceps (Figure 1).

The mediastinoscope, a modified slotted child's esophagoscope, is introduced into the pretracheal space previously prepared by finger dissection. As the scope is passed down the tract, care is taken to keep the anterior tracheal wall in the field of vision at all times. Further paratracheal and carinal dissection can be performed with a specially designed spreader or a forceps modified to hold a small dissecting sponge. Delicate, blunt-tipped laryngeal scissors are used to divide small fibrous bands. Before dissection or division, possible blood-filled structures are identified by means of a long hypodermic needle and aspiration. Sometimes exposed and to be protected are the superior vena cava and azygos veins on the right and on the left, the left pulmonary artery as it crosses the left main bronchus anteriorly, and the descending aorta as it passes behind the left main bronchus. Care also must be taken not to injure the left recurrent nerve which is more ventrally located in the lower tracheal area near the bifurcation. Large pigmented (carbon particles) lymph nodes literally bulge before the orifice of the mediastinoscope as the dissection progresses. Often, masses of matted nodes can be freed and removed intact. The anterior, medial and lateral surfaces of the bronchial walls can be explored out to the pleural reflections. Biopsy specimens are routinely taken of any tumor masses, the paratracheal hilar nodes on both sides, and the subcarinal nodes. The rela-



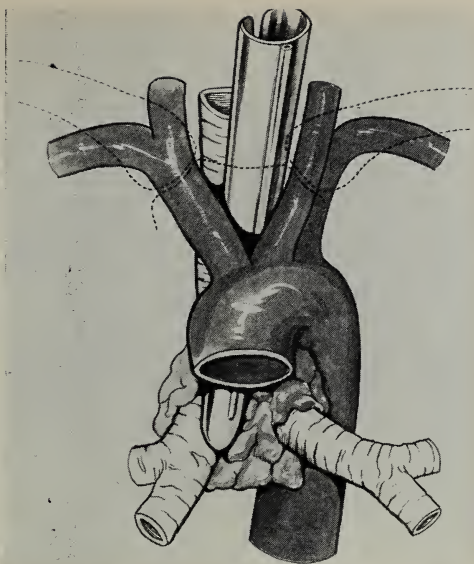


Figure 2.—Diagram of the major anatomical relationships. The mediastinoscope is shown in position to explore and obtain biopsy specimens of the paratracheal and carinal lymph nodes.

tionships of the major mediastinal structures are illustrated in Figure 2.

Cup or basket-type laryngeal forceps are used to obtain the biopsy specimens. In the event of excessive bleeding, gelfoam is placed at the bleeding site and the space is packed. The packing is removed and the gelfoam left in place upon closing. At the completion of the exploration, the mediastinoscope is removed, allowing the mediastinal tissues to fall back against the trachea, thereby providing additional hemostasis. The wound is closed in layers without drainage and a gentle-pressure dressing is applied over the neck incision. The operating time required for performance of mediastinoscopy under local anesthesia is usually 30 to 45 minutes.

Postoperative discomfort is minimal, far less than that encountered after tracheostomy. A number of patients have voluntarily stated that bronchoscopy is more uncomfortable than mediastinoscopy. The patients are encouraged to walk within a few hours after the procedure and may go home in one or two days.

### Indications

As experience with mediastinoscopy has increased, the indications have become more sharply

defined, although they are by no means static. Clinical tests such as blood and culture studies, bronchoscopy and cytology, should be carried out. Where palpable masses or enlarged supraclavicular or neck nodes are readily accessible, biopsy studies of them should be done before resort to mediastinoscopy. In those cases in which all routine clinical studies are normal and mediastinal or hilar masses exist, mediastinoscopy frequently may provide the tissue diagnosis without resort to thoracotomy and its accompanying morbidity and mortality. The merit of mediastinoscopy in determining the spread of carcinoma of the lung to the primary regional lymph nodes has been well documented.<sup>1,3,9,10</sup> In some clinics mediastinoscopy is done in all cases of pulmonary carcinoma to determine the extent of spread of the tumor. The information obtained has often spared patients the expense and risk of unnecessary thoracotomy. The purpose of the procedure is not, however, to determine operability but to obtain information concerning the histological type and the extent of spread. For surgeons who consider extended resection to be worthwhile, mediastinoscopy may yield information on the extent of mediastinal involvement to be encountered at operation. For other surgeons who consider unilateral, contralateral, bilateral, carinal or any combination of positive mediastinal lymph node biopsy as indications of nonresectability, this procedure has much to offer in the selection of patients. For obviously nonresectable cases in which specimens for tissue diagnosis are not available by other means the necessary specimen may be obtained by mediastinoscopy without resort to thoracotomy.

A question often asked is: How often is a positive diagnosis achieved? The answer is that the success or failure of the procedure does not always depend upon a positive histological diagnosis. In some instances a lung lesion is present and the primary objective in performing the procedure is to determine whether there has been metastasis to the mediastinum. In such a case the finding of no metastatic tumor in the lymph nodes provides valuable information concerning the prognosis and possibly the statistical feasibility of accepting the risk of resection in borderline pulmonary cases. In our experience with mediastinoscopy performed to obtain a primary tissue diagnosis or to rule out mediastinal extension of the disease, biopsy of the mediastinal mass and lymph nodes yielded a histological diagnosis in two-thirds of more than 100



Figure 3.—Chest x-ray film (Case 1) showing right upper lobe infiltrate, right hilar mass and mediastinal widening.

cases. The lymph nodes most often contained squamous cell carcinoma (24 cases) or undifferentiated carcinoma (12 cases). Other histological diagnoses included lymphosarcoma, parathyroid-adenoma, one case; adenocarcinoma, two cases; malignant thymoma, one case; lipoma, two cases; noncaseating granuloma (sarcoid), 14 cases; histoplasmosis, four cases; tuberculosis, six cases; acute inflammation, two cases; and lymphoid hyperplasia, 29 cases.

The value of mediastinoscopy can be illustrated by presenting abbreviated histories of some rather typical cases.

### Representative Cases

*Case 1.* A 59-year-old man complained of chest pain and cough of several months' duration. An x-ray film of the chest showed an infiltrate in the right upper lobe and pronounced hilar adenopathy (Figure 3). Results of bronchoscopy and other routine clinical tests including cytology and sputum cultures were normal. Mediastinoscopy was performed under local anesthesia and a large mass extending into the mediastinum along the right hilum was easily palpated. Biopsy and histological study revealed this to be anaplastic carcinoma (Figure 3). The patient was treated with radiation. He died of the disease within six months.

*Comment:* This was a typical case in which clinical laboratory tests were normal and bron-



Figure 4.—Elevated right diaphragm and a small amount of atelectasis of the right lower lobe (Case 2). The mediastinal width appears normal.

choscopy was negative. Mediastinoscopy easily provided a tissue diagnosis without resort to thoracotomy. Without a tissue diagnosis, many radiotherapists would be hesitant to administer radiotherapy.

*Case 2.* A 50-year-old woman complained of shortness of breath and hoarseness of three months' duration. A left radical mastectomy had been performed for adenocarcinoma of the breast eight years previously. X-ray films of the chest revealed no hilar adenopathy (Figure 4). As the airway was compromised, tracheostomy was performed. The dissection was extended into the mediastinum. The mediastinoscope was inserted and biopsy specimens were obtained. They contained adenocarcinoma similar histologically to the breast tumor removed eight years previously.

*Comment:* The absence of hilar enlargement on x-ray films made consideration of other causes for recurrent nerve paralysis essential. Mediastinoscopy permitted early diagnosis and confirmation of recurrent tumor and palliative radiotherapy was administered.

*Case 3.* A 33-year-old woman was seen by her physician for a routine physical examination. Chest x-ray films showed pronounced hilar adenopathy (Figure 5). Routine clinical tests and bronchoscopy were normal. The differential considerations included sarcoid, tuberculosis and



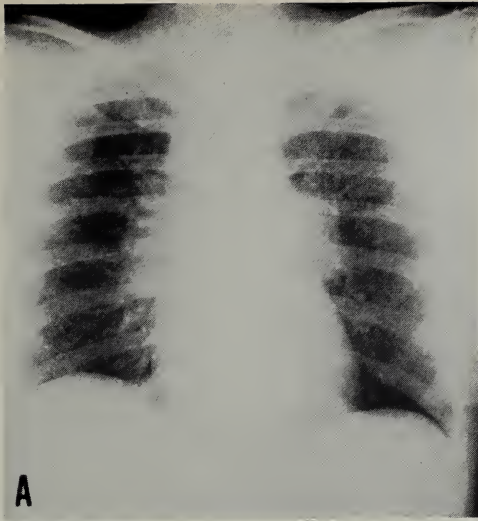


Figure 5. — Film demonstrating hilar adenopathy in Case 3.

lymphoma. Mediastinoscopy was performed under local anesthesia. The lymph nodes in both paratracheal areas and in the carina were enlarged and had the appearance of bluish speckled bird's eggs. This is the classical gross appearance of sarcoid in lymph nodes. Representative specimens were removed, and after sectioning, histological study disclosed noncaseating granuloma compatible with sarcoid.

*Comment:* Mediastinoscopy has proved particularly successful in obtaining histological confirmation when sarcoid tumor was suspected. Bergh and his colleagues<sup>9</sup> used the procedure to establish the diagnosis in 87 percent of cases in which sarcoid was suspected.

*Case 4.* A 44-year-old woman had had pain in the right side of the chest and the sternal area for three weeks. X-ray films showed a rounded mass in the anterior mediastinum causing some indentation of the trachea just above the carina (Figure 6). Bronchoscopy, cytology cultures and other conventional clinical tests were normal. Mediastinoscopy under local anesthesia permitted easy excision of biopsy material under direct vision of the mass, which was located anterior to the trachea. Following histological study, the pathologist reported the tumor to be a malignant thymoma.

*Comment:* This patient was spared the thoracotomy that otherwise would have been necessary

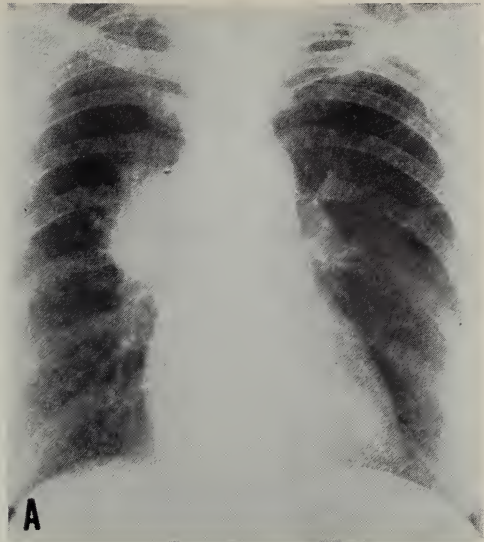


Figure 6. — Anterior superior mediastinal mass and widened upper mediastinum on right (Case 4).

to obtain the tissue biopsy considered essential before radiation therapy. Her response to radiation was excellent, and at last report, five months after diagnosis, she was symptom free.

*Case 5.* A 71-year-old man complained of fever, malaise and weight loss of six months' duration. An x-ray film demonstrated bilateral pulmonary infiltrates with a possible abscess cavity in the right upper lobe. There was no hilar or mediastinal enlargement (Figure 7). Results of routine clinical studies including skin tests, cytology, sputum culture and bronchoscopy were normal. Although the patient's physician believed the pulmonary lesions were metastatic carcinoma, mediastinoscopy was requested in an effort to obtain lymph nodes for histological and culture studies. At mediastinoscopy only small carbon-containing nodes were obtained. Histological examination of the tissue obtained from the mediastinum showed poorly differentiated carcinoma.

*Comment:* Mediastinoscopy in this patient confirmed the clinical impression of carcinoma. While the specific diagnosis was of limited benefit in this case, the possibility that he had a treatable disease was excluded without resort to thoracotomy.

*Case 6.* A 38-year-old man complained of malaise, fever, cough and hoarseness of six weeks' duration. On physical examination he appeared acutely ill. The left vocal cord was paralyzed. An





Figure 7.—Extensive bilateral pulmonary infiltrates (Case 5).



Figure 8.—Large bilobed anterior mediastinal mass (Case 6).

x-ray film showed large bilobed anterior mediastinal masses (Figure 8). Routine clinical examination and tests, including bronchoscopy, were normal. At mediastinoscopy, done under local anesthesia, many enlarged paratracheal nodes were seen. A fixed mass of matted nodes was palpated in the arch of the aorta. A large lymph node was dissected free and a frozen section of it showed lymphosarcoma. Radiotherapy was given.

*Comment:* The patient had smoked heavily (two packs a day) since childhood, and bronchogenic carcinoma was suspected.

*Case 7.* A 62-year-old man was shot in the chest during a fight. The bullet entered the right side of the sternum and lodged in the superior mediastinum (Figure 9). The wound became infected and pus drained from it. On the seventh day after the injury, the bullet was removed by mediastinoscopy under local anesthesia.

*Comment:* This case report was presented to document a previously unreported use for mediastinoscopy.

## Complications

The safety of mediastinoscopy in competent hands has been well documented.<sup>5,11,12</sup> There have been no serious life-threatening complications even though many of the procedures in the more than 100 cases mentioned in this report were performed

by inexperienced residents under close supervision. Pneumothorax developed in two cases. The complication was immediately recognized, as the patients were awake and able to describe their chest pain. Chest tubes were inserted and placed under a water seal. The tubes were removed after 48 hours without sequelae. In four cases of excessive bleeding gelfoam was placed in the area and the wound was packed for five minutes, whereupon the bleeding stopped and the procedure was terminated. In one case the patient was observed to be in respiratory distress at completion of the procedure. He said, in a hoarse voice, that he had no pain. Mirror examination of the larynx with the patient in a sitting position revealed bilateral vocal cord paralysis. As the trachea was easily accessible through the mediastinoscopy incision should the need arise, it was elected to maintain him in the sitting position and await developments. Within an hour and a half the effects of the local anesthetic had passed and both vocal cords had regained normal movement.

In another patient, efforts to dissect with the spreading forceps in a plane at right angles to the slit in the mediastinoscope broke the light bulb from its carrier. Fortunately, the intact bulb stuck in the mediastinoscope and was discovered while preparations were being made for irrigation of the mediastinum. Similar accidents can be prevented

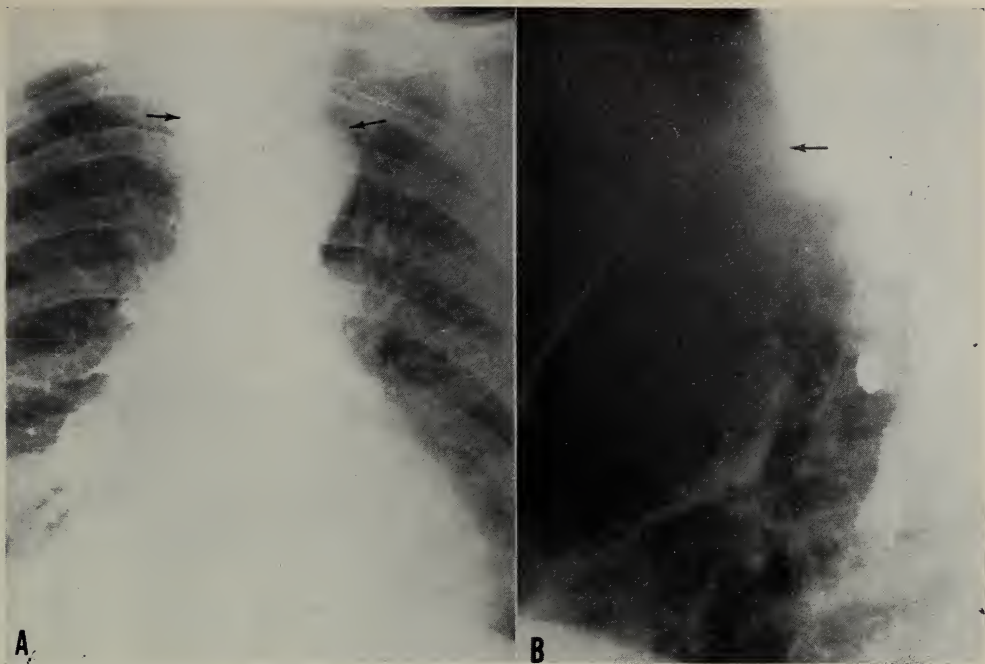


Figure 9.—Chest x-ray films showing bullet (arrows) in the anterior mediastinum (Case 7). The other metallic objects (from a previous fight) were in the soft tissues of the left axilla.

by always dissecting, with a spreading forceps, in the same plane as the mediastinoscope slit. If another plane of dissection is required, the mediastinoscope can be rotated 45 to 90 degrees.

The morbidity and serious complications reported to date are no greater than for scalene node biopsy. The nonfatal complications reported in the literature have included pneumothorax, recurrent nerve paralysis and bleeding from the superior vena cava, azygos vein and bronchial artery. Carlens<sup>11</sup> reviewed some 60 reports comprising more than 4,000 patients and found mention of astonishingly few serious complications. Palva<sup>9</sup> was able to find only two reported deaths up to 1964. One was that of a 67-year-old man in severe respiratory distress with extensive mediastinal metastasis who did not waken from the anesthesia and died one hour after the procedure. The other was that of a 40-year-old woman with lymphosarcoma who died of cardiac arrest immediately after the operation. Bergh and coworkers<sup>9</sup> subsequently reported two deaths in their series of 300 cases. One patient was a 67-year-old man with advanced carcinoma metastatic to the mediastinum who progressively deteriorated and died on the

sixth day following mediastinoscopy. The other was a man 75 years of age who had oat-cell carcinoma and did well until the tenth day when pneumothorax developed. In spite of correction of this problem, he continued to deteriorate mentally and physically, and died on the thirteenth day following the mediastinoscopy. Bergh thought it improbable that mediastinoscopy was directly responsible for either death.

Our experiences, the illustrative cases presented here and those reported by others substantiate the merit of mediastinoscopy as a diagnostic method for diseases of the superior mediastinum and thorax. The success and increased safety achieved by performing mediastinoscopy under local anesthesia should contribute to its increased acceptance in this country as a standard diagnostic procedure.

A question often asked is: Who should perform mediastinoscopy? The answer is that, as in all surgical procedures, it should be done by persons competent in the techniques. They should be interested in studying the disease processes involving the area and be prepared to manage the potential complications. The specific surgical dis-

cipline of the operator is of less importance than are these factors. A surgeon should not hesitate to call on specialist colleagues in the event of complications involving their special area. Although major complications are rare, surgeons performing this procedure should be qualified in managing sternotomy and injured vessels. The latter complications should rarely if ever occur if the correct plane of dissection is obtained and all masses are needled and aspirated before biopsy.

Mediastinoscopy is an important new procedure that the otolaryngologist, the general surgeon, and the thoracic surgeon undoubtedly will include in their diagnostic armamentarium. How large a role the otolaryngologist will assume depends on his interest and competency in performing the procedure. We must gain additional knowledge of the pathologic features and behavior of the various diseases that involve the thorax and mediastinum. Certainly the otolaryngologist's endoscopic training and experience provide him with the sound foundation essential to technical competence in this area. The opportunity to pioneer in this area represents a contribution to medicine. Difficult

problems often can be diagnosed earlier. Many patients with inoperable tumors can be spared the morbidity and mortality that accompany thoracotomy. The simplicity of the technique, the low morbidity encountered, and the valuable information obtainable, suggest that in many instances mediastinoscopy may replace diagnostic thoracotomy.

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## SOLO FIRST AID IN CARDIOPULMONARY ARREST

If a patient has a cardiopulmonary arrest and, as so often happens, there is only one doctor or nurse available, what should he do by himself to support both the cardiac and respiratory systems?

"If a nurse or physician is by himself—and this is not unusual—he should first 'diagnose' the problem (I put diagnose in quotes for the nurses since it's usually against the Nursing Practices Act); he can gain an impression of sudden death or cardiac arrest. He should immediately ventilate the lungs two or three times by mouth-to-mouth ventilation, without calling for any help or anything other than maybe an immediate call, and then immediately perform external cardiac compression for 15 compressions. Then he should ventilate the lungs rapidly, just two quick puffs, expanding the lungs, elevating the chest; then another 15 compressions of the heart externally and two more ventilations—keeping this up. While applying the external cardiac compressions, the nurse or physician can use his lungs to yell for more help."

—JAMES R. JUDE, M.D., Miami

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# CASE REPORTS

## Presumed Transmission of Salmonella by Sigmoidoscope

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SIGMOIDOSCOPY is a common procedure in hospitals and clinics. It is accepted as part of physical examinations and is recommended as a routine office procedure. The potential hazard of transmission of enteric pathogens by use of a sigmoidoscope is generally recognized but actual accidental spread of infectious agents in this manner has not been reported. The present report describes what is presumed to be transmission of *Salmonella* by way of a sigmoidoscope used to examine two patients from different medical wards in a general hospital.

### Report of Patients

Patient A, a diabetic woman 64 years of age, in a state of ketoacidosis, was admitted 22 April 1968 to a diabetic ward for treatment of osteomyelitis of one foot (*S. aureus*, *Proteus*) which developed after a hot water burn. She also had chronic heart failure, pneumonitis, a urinary tract infection (*E. coli*), and fecal impaction. On 30 April the affected leg was amputated above the knee. At that time the patient had a small sacral decubitus ulcer. Four days later, because of constipation she was given an enema (disposable

type) and a large stool was voided. On the following day she complained of rectal pain and was incontinent of blood-flecked feces. In the course of examination on the diabetic ward, the ward sigmoidoscope was used. Biopsy of a specimen of rectal mucosa showed acute and chronic inflammation. A rectal stricture was thought to be present. Three days later, 8 May, the patient was taken to the medical ward for examination and the sigmoidoscope available there was used. Culture of material swabbed from the rectum immediately after the procedure grew *Salmonella lomita*. The mucosa was friable but no focal lesion or stricture was seen. On 10 May a barium enema study was suggestive of segmented colitis. On 11 May (hospital day 19) when results of the culture were known, the patient was transferred to the Communicable Disease Service. She now had a large, unilateral pleural effusion. During the next ten days, without any antibacterial treatment, she had six stool cultures on different days, all of which yielded *Proteus*; none yielded *Salmonella*. Fecal incontinence recurred.

The patient was returned to the diabetic ward 29 May and she died 12 days later. Autopsy diagnoses were pulmonary emboli, pulmonary abscess (*Proteus*, *E. coli*), large sacral decubitus ulcer (*Proteus*, *E. coli*), acute and chronic colitis.

Patient B, a Negro man 71 years of age, entered a medical ward on 4 May 1968 with complaint of cramping abdominal pain and diarrhea for seven days. Dysuria and decreased urine flow had been noted during the preceding month. Examination revealed slight left lower quadrant tenderness and poor rectal sphincter tone. The patient was dehydrated, anemic and incontinent of feces. A urethral stricture was noted. The serum urea nitrogen was 290 mg per 100 ml. *E. coli* and non-hemolytic streptococci, each fewer than 1,000 per ml, were present in urine obtained by catheterization. On 6 May the medical ward sigmoidoscope was used in examination of the patient. Fecal impaction was tentatively diagnosed. Three days

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Submitted 8 July 1969.

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TABLE 1.—Sequence of Events Involving Patients A and B

	Diabetic Ward	Medical Ward
4/22/68	Patient "A" admitted Urine: <i>E. coli</i> Osteomyelitis foot: <i>S. aureus</i> <i>Proteus</i>	
4/30	Amputation, foot	
5/4		Patient "B" admitted Enteritis, urethral stricture
5/5	Sigmoidoscopy Rectal biopsy	Urine: <i>E. coli</i>
5/6	Another patient sigmoidoscoped Lost to follow-up	Sigmoidoscopy
5/8	Patient to Medical Ward for sigmoidoscopy Rectal swab: <i>S. lomita</i>	→
5/9		Urine: <i>S. lomita</i> Beta streptococci
5/11		Another patient sigmoidoscoped Lost to follow-up
5/13		Sigmoidoscopy Fecal specimen: <i>S. lomita</i>
5/15- 5/25	Stool culture: <i>Proteus</i>	
5/20- 5/27		Stool culture: <i>S. lomita</i> Discharged home
6/8	Died	

later, *Salmonella lomita* (more than  $10^5$  bacteria per ml), beta streptococci (less than  $10^3$  per ml) and nonhemolytic streptococci ( $10^3$  to  $10^5$  per ml) were cultured from the urine. Four days later on 13 May (hospital day 10), the patient was again examined and the same sigmoidoscope was used. Culture of the fecal specimen obtained during examination yielded *S. lomita*. On 15 May he was transferred to the Communicable Disease Service. Three more stool specimens obtained during the next week yielded *S. lomita*. The patient was discharged to his home on hospital day 24.

Patient B lived with relatives. Patient A lived alone in an apartment. She drank raw milk. Investigation by the health department did not reveal any additional persons infected with *Salmonella* or other identified source of infection.

The sequence of events described above is outlined in Table 1. The only thing discovered in common for the two patients was exposure to the same sigmoidoscope on the medical ward. The instrument was used for patient B on 6 May and 13 May. *S. lomita* was recovered from stool obtained on the latter date but already had been

found in large numbers in the patient's urine on 9 May and after 13 May was repeatedly found in stool specimens. The same sigmoidoscope was used for patient A on 8 May, at which time *S. lomita* was recovered from a rectal swab. Subsequent stool cultures did not yield this organism.

After use, the sigmoidoscope on the medical ward had been washed with 5 percent Amphyl® (phenols) and then soaked for an unknown period, supposedly 20 to 60 minutes, in 2 percent Staphene® (phenols) after which it was washed with water.

*S. lomita* has not previously been identified during the past six years in this hospital nor in the four-year period in Los Angeles County for which records of *Salmonella* serotypes have been kept. The immediate source of the organism is unknown.

## Discussion

The only environment common to the two patients was the hospital. The only potential mechanism for the transfer of infection discovered in the environment was the sigmoidoscope used for both patients on the medical ward. It was also used for a third patient, lost to follow-up, subsequent to initial use for the two patients who were infected.

Patient B entered the hospital with enteritis. After sigmoidoscopy, *S. lomita* was recovered from his urine and repeatedly from his stools. Possibly the sigmoidoscope was the source of this infection for him. The only isolation of *S. lomita* from Patient A was from a rectal swab taken immediately after sigmoidoscopy on 8 May. The sigmoidoscope was a potential source for the bacteria.

The easiest answer to the problem of disinfection of endoscopes is a disposable instrument. If reused instruments are to be disinfected, the only reliable procedure is autoclaving. Exposure to temperature of 85°C will kill most pathogenic microorganisms<sup>1</sup>; destruction of hepatitis virus at this temperature is not certain.

The American Hospital Committee on Infections Within Hospitals suggests that heat-labile endoscopes be disinfected with glutaraldehyde, formaldehyde solution or ethylene oxide gas.<sup>2</sup> For chemical disinfection of clean lensed instruments, immersion in 2 percent activated glutaraldehyde for ten minutes may be used, or three hours for spores, but "all articles which may carry hepatitis virus should be heat-sterilized."<sup>3</sup> Glutaraldehyde

destroys bacteria including mycobacteria, some viruses<sup>3</sup> and bacterial spores,<sup>4</sup> but its activity for hepatitis virus is unknown. Ethylene oxide gas can destroy bacteria, mycobacteria, bacterial spores and various viruses.<sup>6</sup> It must be realized that irregularities in sterilization can occur with this gas.<sup>2,7</sup> Its action on human hepatitis virus is unknown.

The most readily available recommendations for sanitation of sigmoidoscopes are those given in brochures distributed by manufacturers of these instruments. It is suggested that our distally illuminated instrument (Welch Allyn) can be sterilized by boiling the outer tube and obturator; the inner tube containing a lamp and electrical connection should be washed with soap and water, then wiped with alcohol. Fiber optic models can be exposed to gas sterilization or chemical cold sterilization (except Lysol® compounds). American Cystoscope Makers suggest cleaning, then immersion in a 1:1,000 quaternary ammonium compound, for instruments that do not have fiber optics. The latter, after cleaning, are washed or swabbed with the quaternary solution or 50 percent alcohol. Both manufacturers also have autoclavable fiber optic models.

Mycobacteria are resistant to quaternary ammonium compounds; certain bacteria, particularly Gram-negative ones such as *Pseudomonas* and

*Proteus*, tend to be resistant; bacterial spores are resistant.<sup>2,8,9</sup> The sensitivities of human hepatitis viruses are unknown. Quaternary ammonium compounds are inadequate for disinfection of endoscopic instruments and should not be used for this purpose. At present the only method proved reliable is autoclaving. The alternative is a disposable instrument.

#### TRADE NAMES AND GENERIC INGREDIENTS

*Amphyl*® . . . . . phenols, ricinoleate, propylene glycol and alcohol  
*Staphene*® . . . . . phenols, isopropanol, tetra-acetate and laurate  
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#### WHAT KIND OF ORAL CONTRACEPTIVE?

"I want to . . . point out that there should be no blanket favoritism for any one oral contraceptive drug over another, that one must individualize for a given patient. If you have a thin patient who wants to gain weight, you give her a combination with lots of estrogen and lots of progestin in it; if you have a girl who has hypomastia and thinks she could stand a little improvement, you try to give her a pill with lots of estrogen and not too much progestin in it; if she's got hypermenorrhea, a combination is preferable to a sequential; if she tends to hypomenorrhea or amenorrhea, a sequential is preferable."

—JOSEPH W. GOLDZIEHER, M.D., San Francisco  
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## Progress in Birth Defects Research

MERTON R. BERNFIELD, M.D., *Stanford*

DEVELOPING ORGANISMS traverse a series of gene-directed sequential changes in morphology and metabolism. Abnormal development occurs because of alterations in the genome or as a result of extrinsic influences. Research into the causes and consequences of abnormal development has received great emphasis in recent years. Much of the current interest has been stimulated by progress in genetics and in molecular and developmental biology. To understand some significant advances in birth defect research, it is necessary to know something about recent progress in these areas of basic science. I have therefore briefly reviewed some of this work and have presented it in relation to its importance to birth defects research. Specific references have not been included to support the basic science work cited, but the reader is referred to reviews and monographs for extensive discussions of those studies.

The mechanism of gene action has been recently clarified.<sup>1,2</sup> The information carried by a gene is determined by its sequence of nucleotide bases, which via a series of intervening steps dictate the sequence of amino acids in proteins. It is the amino acid sequence of a protein that determines the overall structure and function of the molecule, whether it be a structural protein or an enzyme. The DNA nucleotide bases are enzymatically transcribed into a complementary sequence of bases in RNA molecules. Although all RNA is made in this

manner, the form of RNA used to direct the synthesis of proteins is messenger RNA. This RNA serves as a template which dictates the sequence of amino acids. The initial steps in protein synthesis occur in the cytoplasm where each amino acid is linked to a specific RNA molecule, called transfer RNA. The amino acid-transfer RNA complex recognizes specific nucleotide sequences on the messenger RNA. In this way, the amino acids are linked together enzymatically in the order determined by the messenger RNA, and consequently the gene.

The major problems of developmental biology are central to birth defects research. These are (1) how does a single cell (the fertilized zygote) give rise to the organism's many specialized cell types, and (2) by what mechanism do developing tissues influence the course of development of other tissues. We are far from answering these questions, but considerable insight into gene activity during development has become apparent from recent studies. By inserting a nucleus from a highly differentiated cell into an unfertilized egg whose nucleus has been removed, Gurdon and his collaborators showed that the transplanted nucleus retains the genes necessary for the specialization of all cell types.<sup>3</sup> Consequently, specialization of cells does not involve the selective elimination or permanent inactivation of genetic material. By transplanting nuclei from embryonic tissue at various developmental stages into either eggs or their oocyte precursors, it was found that the cytoplasmic components of these cells bring about changes in the gene activity of the transplanted nuclei. The means by which the cytoplasm influences gene activity remains to be clarified.

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Advances in the understanding of early embryogenesis have resulted from studies on protein and RNA synthesis subsequent to fertilization.<sup>4,5</sup> It has become abundantly clear that, at least in echinoderm and amphibian zygotes, embryonic development prior to the formation of the primordial germ layers is under the direct influence of maternal genes. During this early embryogenesis, the developing embryo utilizes messenger RNA and other components of protein synthesis which have been made in the egg and are therefore of maternal origin. Despite utilization of maternal messenger RNA, the fertilized egg produces its own gene products, but this newly-synthesized RNA may be masked in some way and temporarily inactive in protein synthesis. Since early embryogenesis is sustained and directed by maternal genes, it might be expected that maternal genetic defects may have an effect upon the progeny, regardless of the genetic constitution of the embryos themselves. It is not known whether early mammalian embryogenesis is under the influence of maternal genes and whether there is masked messenger RNA. The available evidence is not sufficiently clear to provide an answer.

### The Genetics of Birth Defects

A significant advance in our understanding of heredity was the establishment of the nature of the genetic code.<sup>6,7</sup> It was theorized that a series of three nucleotide bases on DNA coded for each amino acid: this coding unit was called a codon. There are four different nucleotide bases in DNA (and in RNA as well) and, consequently, there are 64 (4 to the third power) possible three-base codons. In a series of brilliant experiments for which they shared (with R. W. Holley) the 1968 Nobel Prize in Medicine, Nirenberg, Khorana and their coworkers established the codon base sequences which indicate the amino acids. Although these studies were performed with microorganisms, the nucleotide codons are identical in all living systems. The genetic code allows a more precise understanding of how genetic defects or mutations may result in abnormal proteins. For example, hemoglobin S, the hemoglobin of sickle cell anemia, is abnormal in that its  $\beta$ -chain contains a valine instead of a glutamic acid at residue number 6. Inspection of Table 1 reveals that the gene for sickle hemoglobin contains an adenosine in place of the normal thymidine in the DNA codon for this

TABLE 1.—Alterations in the Hemoglobin Gene

Hemoglobin Type	$\beta$ -chain Amino Acid at Position 6	Messenger RNA	Gene
		RNA codon	DNA codon
S	Valine	GUA	TAC
		↕	↕
A	Glutamic Acid	GAA	TTC
		↕	↕
C	Lysine	AAA	TTT

position in the sequence. Similarly, there is a single nucleotide base change from normal in the gene for hemoglobin C, which contains a lysine at the sixth position. The nucleotide alteration in the gene is reflected in the complementary, but antiparallel, messenger RNA sequence. Mutations of these types are called structural gene mutations, because the sequence of amino acids (or primary structure) of the protein is altered.

Structural gene defects are frequently manifested as enzyme deficiency states, inasmuch as the enzyme protein with an amino acid substitution frequently (but not always) has little or no enzymatic activity. Examination of the genetic code (Table 2) indicates that the codon assignments exhibit a high degree of order. Functionally related amino acids have similar codons and, except for tryptophan and methionine, each amino acid has more than a single codon. The nature of the code ensures that a significant proportion of mutational events results in no or minimal change in the amino acid sequence. In diploid organisms, such as man, the effect of a structural gene mutation is frequently not observed. The individual carries a normal gene in addition to the mutant gene, and usually the defect becomes clinically significant only in the presence of two identical alleles, the homozygous state. The individual who is heterozygous for the structural gene defect will frequently demonstrate a level of the gene product which is intermediate between the normal and the homozygous state. The current status of the detection of heterozygous carriers for structural gene defects has been reviewed by Hsia.<sup>8</sup>

A powerful technique for the detection of enzyme deficiencies was recently developed by Murphey and Guthrie utilizing the Beutler technique.<sup>9,10</sup> The method is relatively simple and is particularly well suited for the screening of large populations. A few drops of blood from a fingertip are dried on a specially prepared filter paper,

TABLE 2.—*The Genetic Code*

UUU	Phenylalanine	UCU		UAU	Tyrosine	UGU	Cysteine
UUC		UCC	Serine	UAC		UGC	
UUA	Leucine	UCA		UAA	Termination*	UGA	Termination*
UUG		UCG		UAG		UGG	Tryptophan
CUU		CCU		CAU	Histidine	CGU	
CUC	Leucine	CCC	Proline	CAC		CGC	Arginine
CUA		CCA		CAA	Glutamine	CGA	
CUG		CCG		CAG		CGG	
AUU		ACU		AAU	Asparagine	AGU	Serine
AUC	Isoleucine	ACC	Threonine	AAC		AGC	
AUA		ACA		AAA	Lysine	AGA	Arginine
AUG	Methionine	ACG		AAG		AGG	
GUU		GCU		GAU	Aspartic Acid	GGU	
GUC	Valine	GCC	Alanine	GAC		GGC	Glycine
GUA		GCA		GAA	Glutamic Acid	GGA	
GUG		GCG		GAG		GGG	

\*Termination is the genetic punctuation mark for "stop translating."

which can be mailed to a central laboratory. The blood spots are eluted with an appropriate buffer and the eluate assayed for enzyme activity. Utilizing this technique, a great number of red blood cell enzymes can be detected, some of which have been associated with enzyme deficiency states in man. These enzyme deficiency states are predominantly those associated with congenital non-spherocytic hemolytic anemia. Red blood cells are highly differentiated and may not contain many enzymes present in other tissues. Leukocyte enzymes provide a better index of parenchymatous organ enzyme deficiencies. Selective sedimentation of red blood cells with dextran-salt solutions<sup>11</sup> yields relatively pure, viable leukocytes which can be used for the detection of enzyme abnormalities. Legum and Nitowsky have presented a resume of disorders detected by analysis of leukocyte enzymes.<sup>12</sup>

Although it is relatively easy to see how an abnormal metabolic event may occur as a consequence of a structural gene mutation, there have been attempts to invoke control gene mutations as a cause of metabolic errors in man. The concept of control-gene disease stems from microbial genetics where several types of regulatory genes and

mutations have been elucidated. Control genes are physically distinct from the structural genes, but regulate their activity. In general, mutations in control genes result in alterations in the quantity but not the quality of the affected protein. It is unclear at present whether there are diseases in man due to regulatory gene defects. Proof of a control gene mutation rests with demonstrating that the small amount of enzyme synthesized is of normal structure. In addition, the mutation should be in a site distinct from the structural gene for the enzyme in question. The latter requirement requires locating the gene loci on chromosomes.

Although there has been considerable work on linkage of autosomal traits, it is only quite recently that proposed assignments of gene loci to specific human chromosomes have been made.<sup>13</sup> These beginnings in the mapping of human autosomes were made possible by the observation that a specific chromosomal variation of chromosome 1 was linked to two other closely linked genetic traits.<sup>14</sup> The method of assigning loci based on linkage tests is useful, and further information will be obtained in the future by combining linkage analysis with studies of patients with unbalanced chromosome constitutions. Study of interspecific



cell hybrids shows great promise for the mapping of human chromosomes. This method has been used for identifying a locus for thymidine kinase on chromosome No. 17 or 18.<sup>15</sup> Cell hybrids can be derived from the fusion of individual cells. Under the appropriate conditions, nuclear fusion may occur, producing mononuclear cells which may be capable of sustained proliferation. Following hybridization, the chromosomes from both parental lines may be identified by karyotypic analysis. With further culturing, there generally is a reduction in chromosomal number which is of a non-random nature. For example, Weiss and Green<sup>16</sup> noted that a mouse-man hybrid cell culture successively discarded mainly human chromosomes. In general, the loci of both parental genomes function and produce gene products in the hybrid cell. Utilizing appropriate cell lines for parental strains in making the hybrid cell, special culture media may be used for growing the hybrid clones and selecting for particular genotypes.<sup>17</sup> Such studies may be used to identify autosomal loci and, even more importantly, may provide a useful technique for performing somatic cell genetics in tissue culture.

Knowledge of sex-linked disorders in man has contributed greatly to investigations of the x-chromosome.<sup>18</sup> Studies of gene linkage and assignments of loci have been made for the x-chromosomes, largely due to investigations of patients with x-chromosome structural anomalies and aneuploidy.<sup>19</sup> The suggestion, in 1961, that one of the two x-chromosomes in the cells of normal females is genetically inactive has been amply confirmed.<sup>20</sup> This x-chromosome inactivation provided evidence for gene dosage compensation in the female, allowed a further understanding of the inheritance of x-linked genes, and led to many studies of gene inactivation during embryonic development.<sup>21</sup>

## Multiple Gene Defects

Although a number of hereditary abnormalities are due to single gene defects, other abnormalities undoubtedly occur by the concerted action of more than a single gene (polygenic or multifactorial inheritance). Polygenic inheritance is best established for characters showing continuous quantitative variation—for example, intelligence, stature, blood pressure and skin color. Genetically determined birth defects which probably result from the action of several genes include congenital dislocation of the hip, hypertrophic pyloric stenosis, vari-

ous forms of club foot, cleft lip with or without cleft palate, and atrial septal defect.<sup>22-24</sup> Penrose,<sup>25</sup> however, has suggested that it is extraordinarily difficult to distinguish the effects of multiple genes from the effect of a single locus with a great many alleles, each of which provides a distinct quantitative increment. Carter recently summarized the evidence for a polygenic mode of inheritance for these malformations.<sup>24</sup> One means of analysis is the study of twins for concordance, the simultaneous occurrence of the trait in both twins. For each of these abnormalities, the concordance in monozygotic twins is five to ten times greater than in dizygotic twins.<sup>22</sup> However, the concordance never exceeds 50 percent, even in monozygotic twins. Monozygotic twins arise from the same zygote and, by definition, have an identical genetic complement. Consequently, it is difficult to comprehend why such twins are not fully concordant for a genetic trait. Additional prenatal environmental factors which in some way interact with the genetic predisposition have been suggested to account for this paradox.<sup>26</sup>

Polygenic inheritance implies that there is a complex of genes which interact to produce a particular abnormality and that these genes must be present in a specified quantity in order to produce their effect. This threshold effect has been tested by Carter in his analysis of the inheritance of congenital hypertrophic pyloric stenosis<sup>27</sup> and congenital dislocation of the hip.<sup>24</sup> The postulate is that if there is a sex difference in the disease frequency (as in these two disorders) there will be higher incidence of the abnormality in relatives of the sex which shows the lower incidence of the abnormality. If the genes which are responsible for the defect are operating additively, then more genes (a higher threshold) will be required in the individual whose sex protects against the defect. For example, since the incidence of congenital dislocation of the hip is at least five times greater in women than in men, then there should be a higher incidence of congenital dislocation of the hip in the children born to an affected male than in children born to an affected female. The opposite would be true in the case of hypertrophic pyloric stenosis, in which there is approximately a five-fold greater incidence in males. Consequently, more genes (a higher threshold) would be required to produce the defect in a female. By examination of Table 3, one can see that a much greater frequency of pyloric stenosis occurs in the children

TABLE 3.—Frequency of Pyloric Stenosis in Children of Affected Individuals

Parent Who Had Pyloric Stenosis	Total No. of Children	Children With Pyloric Stenosis			
		Sons		Daughters	
		No.	%	No.	%
Mother	80	9	20	4	11
Father	323	11	6.8	2	1.2

Based on data from Carter.<sup>27</sup>

of an affected mother than in the children of an affected father.

In comparison with single structural gene defects which usually are detected as enzyme deficiency states, polygenic inheritance is studied in man with statistical tools. Several means for the testing of data for the presence of polygenic inheritance are available, and a number of theories have been put forward to explain this mode of inheritance.<sup>24,28</sup> Of great significance, however, is that manipulation of the environment may readily alter the phenotype of a polygenic trait. An instructive example as to how such environmental factors might play a role has come from the work of Kalter on teratogenesis in isogenic strains of mice. These experiments were performed with a strain of mice which develop cleft palate in high percentage after the administration of prednisolone at a particular time of gestation. Kalter<sup>29</sup> examined the incidence of cleft palate in the fetuses which lay next to an embryo with cleft palate and compared this data with the incidence of the abnormality in fetuses which were next to an unaffected embryo. The data of Table 4 indicate that there is a nearly two-fold greater incidence of cleft palate in fetuses which were proximate to affected embryos. This example of the interaction of a genetic predisposition (as suggested by the special strain of mice), and the environment (in this example, a known teratogen in mice) was modified in some manner by the micro-environment of the uterus, so that apparently "hot spots" of teratogenic action were present in the mouse uterus.

### Chromosomal Abnormalities

Human cytogenetics is a well-defined discipline and chromosome abnormalities and their associated clinical syndromes have been the subject of recent reviews.<sup>30-32</sup> Chromosome abnormalities have been estimated to occur in nearly one zygote in ten, accounting for about one-quarter of spontaneous abortions.<sup>33</sup> The most common anomalies

TABLE 4.—Frequency of Prednisolone-Induced Cleft Palate According to Intrauterine Location

Location of Fetus	Fetuses with Cleft Palate			
	Group 1		Group 2	
	No.	%	No.	%
Next to Fetus With Cleft Palate	133	58.3	357	85.4
Next to Normal Fetus	95	32.4	63	50.0

Based on data from Kalter.<sup>29</sup>

in spontaneous abortuses are autosomal trisomy, polyploidy and monosomy-X.<sup>34</sup> The etiology of chromosomal aberrations is unclear.<sup>35,36</sup> It has been known for many years that there is a correlation between maternal age and the frequency of Down's syndrome. Recent data also suggest a relationship between maternal age and the incidence of other autosomal trisomies, XXV males and XXX females.<sup>37</sup> The reason why nondisjunction is associated with conception in older women is not known.

German<sup>38</sup> proposed delayed fertilization as being a cause of nondisjunction. He assumed that with advanced maternal age and in marriages of longer duration, there would be a decreased frequency of coitus and consequently an increased interval between ovulation and fertilization. This delay, it was postulated, leads to a deterioration of the ovum, resulting in meiotic nondisjunction. However, Penrose and Berg<sup>39</sup> found no relationship between the incidence of Down's syndrome and the duration of marriage. Other workers have reported errors in the mathematical formulation originally proposed by German.<sup>40,41</sup>

In a retrospective study, Sigler, et al<sup>42</sup> compared the radiation exposure of mothers of children with Down's syndrome with those of controls and presented evidence suggesting that radiation exposure may play a role in nondisjunction. There is a recent report<sup>43</sup> of an extensive prospective study in which children conceived after maternal radiation exposure were compared with maternal-age-matched children conceived before exposure. The data revealed that a greater number of trisomic children were born after maternal exposure. This increased susceptibility to nondisjunction was associated with an increase in maternal age. A possible explanation for the maternal age effect has been advanced by Henderson and Edwards.<sup>44</sup> They observed a decrease in the frequency of chiasmata in oöcytes of elderly mice. Maternal auto-immunity has frequently been implicated in



the etiology of chromosomal aberrations. In particular, antithyroid antibodies have been implicated by the studies of Fialkow.<sup>45</sup>

Recently, considerable interest has been evidenced in spontaneous chromosomal breakage as a cause for structural chromosomal abnormalities. Ionizing radiation causes an increased frequency of chromosomal aberrations in lymphocytes,<sup>46</sup> and viruses can produce similar effects.<sup>47</sup> The list of agents which can produce chromosomal abnormalities has recently been expanded to include lysergic acid diethylamide (LSD)<sup>48,49</sup> and calcium cyclamate, the sugar substitute.<sup>50</sup> Stable and unstable chromosomal abnormalities are noted in the cultured lymphocytes.<sup>37</sup> The unstable aberrations include dicentric and ring chromosomes, as well as acentric fragments. The stable aberrations include inversions and reciprocal translocations. Unstable aberrations increase the probability that the affected cell will not survive an ensuing cell division. However, these abnormalities are quite easily detected cytologically. In contrast, the inversions and reciprocal translocations are less apparent and have a greater likelihood of being maintained through subsequent cell divisions. Some lymphocytes may survive long periods *in vivo*, with mean survival time being estimated to be as long as five years.<sup>51</sup> Although the effects of various agents may be assessed by examination of lymphocyte chromosomes, the presence of chromosomal abnormalities in these somatic cells cannot be transformed at present into mutagenic risks to germinal cells.

In the past few years considerable emphasis has been placed upon ascertaining the frequency of chromosomal aberrations in the normal population. Such studies are of importance because morphologic chromosomal abnormalities have not been closely integrated with established quantitative serologic or biochemical techniques. Most of the work in human cytogenetics has involved study of selected abnormal individuals from which a correlation was established between phenotype and karyotype. Few studies have characterized structural chromosomal variations unassociated with phenotypic abnormalities. It is difficult to determine whether an unusual chromosomal rearrangement is causally related to the phenotype in a malformed infant.<sup>52</sup> Karyotypic analysis of unselected newborns on a mass basis must serve as reference material (see references 53-56) for studies of the effect of variation in chromosomal

morphology and phenotype. The introduction of densitometric scanning techniques linked with computer analysis will make these studies more feasible.<sup>57</sup>

The frequency of individuals in the general population who are heterozygous for structural chromosome abnormalities may be as high as three per thousand.<sup>37</sup> Although several examples of balanced translocation have been detected in surveys of normal human populations,<sup>58</sup> many more probably exist than are at present detectable. A high proportion of children who are found to have unbalanced karyotypes are the offspring of parents whose somatic chromosomes are apparently normal. The converse is also undoubtedly true; individuals with apparently normal karyotypes may have unbalanced genomes.<sup>59</sup>

### Intrauterine Infections

There is growing concern and much investigative effort directed toward the prenatal period of life. The fetus and its intrauterine environment have been the subject of several recent volumes.<sup>60-62</sup> The remarkable contributions of Liley, Clarke, Freda and their coworkers on intrauterine diagnosis and therapy, and on the prevention of Rh-isoinmunization will not be reviewed here. The reader is referred to detailed accounts of this work.<sup>63-65</sup>

A great deal of work has been done in recent years on investigations of the relationship of maternal infections to birth defects. The most dramatic of these have been the studies on congenital rubella. In 1962, rubella virus was isolated and grown in tissue culture,<sup>66,67</sup> allowing the development of precise serologic techniques for the detection of rubella infection.<sup>68-70</sup> These techniques were utilized in studies of the 1964-65 rubella epidemic during which approximately one percent of pregnancies became rubella casualties (see reference 71). As a result of a collaborative study in which more than 6,000 women were investigated, the natural history of postnatal and congenital rubella was clarified.<sup>72</sup> The relationship between maternal rubella, the risk to the fetus, and specific congenital anomalies was recently reviewed.<sup>73,74</sup> Congenital rubella is a chronic disease, and affected infants remain infected for months after birth. This chronicity is in contrast to postnatal rubella, which has raised speculation regarding the possibility that defective<sup>75</sup> immune mechanisms may exist in the infant with intrauterine-acquired rubella.

It is clear that antibody response to congenital



rubella infection occurs regardless of the time of fetal infection. Most infants respond to congenital rubella with the production of IgM as well as IgG antibodies in normal sequence.<sup>76</sup> Despite the apparently normal humoral antibody response there is some evidence that cellular immunity in congenital rubella infections may be abnormal. Functional defects of peripheral lymphocytes derived from children with congenital rubella have been described.<sup>77,78</sup> Very few inflammatory changes are seen in infants with congenital rubella, and certain organs are reported to have a subnormal number of cells.<sup>79</sup> The consequences of rubella infection are not clearly understood. The virus inhibits mitosis and increases chromosomal breaks in human embryonic cells grown in tissue culture.<sup>80</sup> Cells grown from tissues derived from fetuses infected with the virus grow more slowly in culture.<sup>81</sup>

Most recently a great deal of excitement has surrounded the licensing of a rubella vaccine. Symposia on rubella vaccines were held in London in November, 1968,<sup>82</sup> and in Bethesda in February, 1969.<sup>83</sup> Several reports on the use of rubella vaccines have been published. Parkman and his co-workers performed extensive studies with a strain of rubella virus attenuated by 77 tissue culture passages in African green monkey kidney cells.<sup>84</sup> This strain of vaccine, designated HPV-77, adapted to grow in duck embryo cells, has been used in the most extensive clinical trials. The vaccine is highly effective. Seroconversion rates are approximately 95 percent. There are few complications of the vaccine in children, and, although the virus is excreted from the throat, no spread of the virus to susceptible contacts has been observed. Transient arthritis and paresthesias have been observed in vaccinated adults, especially women. The effect of the attenuated rubella virus on the fetus has not been adequately evaluated.

The USPHS Advisory Committee on Immunization Practices, in conjunction with the Committee on Control of Infectious Diseases of the American Academy of Pediatrics, has prepared a prelicensing statement for the use of live attenuated rubella vaccine.<sup>85</sup> They recommended that the initial priority for immunization be children in kindergarten and the early grades of elementary school in an attempt to eradicate the major source of virus dissemination in the community, and ultimately to prevent infection in the population at risk—pregnant women and women of childbearing age. Children between age one and puberty

may receive the vaccine. Pregnant women should not be given the vaccine. Women of childbearing age may be considered for vaccination only when the possibility of pregnancy in the ensuing two months is essentially nil. Immunization of post-pubertal females should only be undertaken on an individual basis, and optimally after serological testing for susceptibility to rubella.

It remains to be seen whether or not rubella vaccination will remove the main reservoir of endemic infection. The vaccination of children to protect mothers in an attempt to break the chain of transmission is a unique approach. It will be mandatory to follow the duration of immunity in the vaccinated children, since there is little advantage in this approach if immunity becomes less protective when the vaccinated children reach childbearing age. Nonetheless, the probability of completely eradicating this major cause of birth defects is on the horizon.

What is the available evidence concerning the role of other viral infections in the etiology of congenital malformations? A number of studies have been done utilizing specific serological and virological tests.<sup>86-88</sup> In general, these studies reveal no differences in the number of congenital anomalies, stillborns, or abortions among persons with serological evidence of infection during pregnancy with several coxsackie B and A strains, ECHO viruses, as well as adenovirus and influenza type A and B. The evidence that intrauterine mumps or coxsackie infections may be responsible for endocardial fibroelastosis is inconclusive.<sup>89-91</sup> Prospective serologic evidence for an association between first trimester coxsackie B (types 3 and 4) infection and various forms of congenital heart disease has been reported by Brown and Evans.<sup>92</sup>

The role of intra-uterine infections as a cause of developmental malformations has been summarized in a recent symposium.<sup>93</sup> It has recently been demonstrated and confirmed that elevations of IgM globulin in cord blood may reflect chronic intra-uterine infection.<sup>94,95</sup> However, elevation of the 19-s globulin may be nonspecific and may be associated with a variety of infections, some of which may not be of clinical significance.<sup>96</sup> Cord blood IgM values of infants with documented congenital infection cannot always be distinguished from values in uninfected infants. Consequently, whenever possible, specific antigens should be tested in each instance of an elevated IgM level.<sup>97-99</sup> An elevated cord blood IgM level, however, may

be a useful indicator of subsequent disability in infants who appear normal at birth.<sup>100</sup>

Hanshaw found a significant incidence of cytomegalovirus complement-fixing antibody in children with microcephaly.<sup>101</sup> However, the prevalence of cytomegalovirus infection in the general population is not well established. Hanshaw reported that 18 percent of normocephalic persons have cytomegalovirus complement-fixing antibody in their serum, whereas Sever et al reported that 30 to 60 percent of pregnant women studied had detectable complement-fixing antibody.<sup>102</sup> From 4.3 to 7.7 percent of these women showed a significant increase in their titer during pregnancy; a significant number of pregnancies are undoubtedly complicated by cytomegalovirus infection.<sup>103</sup>

At a recent meeting of the Society for Pediatric Research, Starr, Bart, and Gold reported on a clinical assessment of infants with established inapparent congenital cytomegalovirus infection.<sup>104</sup> These workers attempted virus isolation from the urine of more than 2,500 consecutive newborns and found viruria in a ratio of 1:83. There was no apparent seasonal variation or socioeconomic prevalence. The infants excreting virus were compared with a control group of infants and were followed for periods up to 15 months at the time of the report. Infants excreting virus had lower average birthweight and had younger mothers. However, there were no significant differences in head circumference, weight at follow-up, length, or developmental quotient. There was no difference between the groups in neonatal morbidity, as determined by the length of hospital stay, or in the presence of congenital malformations. All infected infants continued to excrete the virus even up to 15 months postnatally, while the mothers, if they had viruria at the time of delivery, stopped excreting the virus during the period of observation. A number of features of this study require confirmation, and continued follow-up studies may be particularly revealing. Nonetheless, it is clear from this investigation that neonatal virus excretion can mean clinically inapparent intra-uterine infection, just as in postnatal viral infection.

### Extrinsic Influences on Development

Various environmental agents have been suspected of leading to birth defects. Regardless of the agent affecting the fetus, fetal age is the predominant factor in determining the teratogenicity of the offending circumstance.<sup>105</sup> Before the for-

mation of the primary germ layers (approximately the end of the second week in man), the embryo is usually not susceptible to teratogenesis. However, during the period of early differentiation, the organism becomes highly susceptible to the action of many agents. In general, the effects of the noxious agent will depend upon the stage of development of the particular organ or tissue. The nature of the abnormality is also dependent upon the character of the agent, its dose, and its presumed mode of action. After the completion of the period of differentiation (about the end of the fifteenth week in man) the fetal organism becomes increasingly resistant to the effects of potential teratogens.

A major problem in teratogenesis is that the fetal organism is qualitatively different from the mature organism or even the neonate. Several enzyme systems, including the drug metabolizing enzymes of the endoplasmic reticulum,<sup>106</sup> develop late in gestation. Consequently, relatively benign agents in the mature organism may be quite destructive to the fetus. The qualitative difference between the fetal and mature organism is illustrated by the fact that except for the cytotoxic anti-cancer drugs,<sup>107</sup> the postnatal pharmacologic properties of a drug are rarely mirrored in its teratologic effects.<sup>108</sup> Chemical agents which affect the fetus must traverse the placenta. It has become apparent that, with the exception of a few highly charged ionic compounds (for example, neuromuscular blocking agents) or certain large molecular weight compounds (albumin, for example), most drugs given to the mother in therapeutic amounts reach the fetus.<sup>109</sup> The placenta, however, may alter the drug, rendering it pharmacologically inert.

Karnofsky<sup>110</sup> has stated that "any drug administered at the proper dosage and at the proper stage of development to embryos of the proper species . . . will be effective in causing disturbances in embryonic development." It is indeed surprising that so few agents are known to be teratogenic in man. A drug or situation which is demonstrably teratogenic in animals may not be so in man, and the converse is similarly true. Hence, the proof of whether an agent is responsible for the causation of human congenital malformations must be sought in man.<sup>111</sup>

The developmental effects of radiation, including those reported by Neel<sup>112</sup> on his extensive studies of the survivors of the atomic bomb holo-



causts, were recently reviewed.<sup>113</sup> In man, exposure to large amounts of radiation produces developmental abnormalities. Microcephaly is an almost constant feature, while other abnormalities are, in general, related to the gestational age of the fetus at the time of radiation exposure. Extensive analyses of the A-bomb survivors for delayed genetic and teratologic effects of radiation exposure have produced little substantial evidence that radiation has major long-term developmental consequences.

Since the thalidomide incident in the early 1960's, there has been increasing awareness of the possibility of drug-induced malformations. The available evidence implicating drugs as a major cause of birth defects is meager. Mellin performed a prospective epidemiologic study of the possible effects of drugs during pregnancy.<sup>114</sup> The study was performed in the period 1953-1957, before the thalidomide incident and its effect on the attitudes of the medical as well as the lay population. Thirty-two hundred pregnant women were registered in the first trimester. At intervals, the women were queried regarding the nature and the amount of drugs taken. The pregnancies which resulted in infants with any birth defect (a total of 266) were compared with a control group of pregnancies taken at random. Analysis revealed that there was no difference in the total number of drugs or the specific types of drugs taken during pregnancy between the two groups of women. When the data as to major malformations were analyzed, no specific drugs could be identified as causing a specific malformation. Nearly half of the mothers in both groups had taken no drugs during pregnancy. Mellin concluded that "drugs in general . . . are not important factors in malformations in general." This study, although extensive, was dependent upon the mothers' recollection of drug intake and upon the physician-interviewer's diligence.

Recently, Nora et al reported information on a group of closely-observed pregnant women who were followed by the same group of physicians in a prospective fashion.<sup>115</sup> Two-hundred and forty women in any stage of pregnancy were registered, although over half of them were in the first trimester. The investigators established 102 categories of potential teratogens and ascertained at frequent intervals whether the women were exposed. No significant differences in the number of congenital anomalies were noted between infants exposed in the first trimester to any of the potential

teratogens and those with no such exposure. Infants with documented first trimester exposure to specific agents (for example, radiation, appetite suppressants, tranquilizers, anti-nausea preparations) showed no greater incidence of abnormalities than those exposed to the same agent later in gestation. It is apparent from these studies that it is difficult to ascertain the role of potential teratogenic agents in the causation of human malformations. It is probably incorrect to conclude that there are no significant effects of radiation or drugs upon human fetal development; it is more likely that identification of teratogenic agents is extraordinarily difficult.

One possible explanation for the lack of clear-cut evidence regarding the influence of various potential teratogens on the development of congenital malformations, is that the potential teratogen may produce a developmental abnormality only in an individual with an hereditary predisposition.<sup>116</sup> Since malformation resulting from the action of teratogens occurs only at discrete developmental periods, and possibly only in an individual with a permissive genotype, it is not surprising that random population studies fail to document the extent of drug teratogenicity. Case reports of isolated instances implicating a particular teratogenic agent by mere association of the drug taken during pregnancy are of little significance. For example, the incidence of developmental abnormalities is approximately 2 percent, and if 5 percent of all pregnant women take a drug (for example meclozine, an agent widely used for treatment of nausea and vomiting of pregnancy) then, on a coincidence basis alone 1 in 1,000 pregnancies will be associated with both meclozine and an infant with a birth defect.<sup>108</sup> Association of this type caused the drug to be with-

TABLE 5.—Teratogen-Induced Cleft Palate in Various Mouse Strains

Parental Strains*		% of Progeny with Cleft Palate	
Mother x Father	Progeny	Cortisone	6-aminonicotinamide
crosses			
A <sup>S</sup> x A <sup>S</sup>	A <sup>S</sup>	100	76
C <sup>R</sup> x C <sup>R</sup>	C <sup>R</sup>	17	11
A <sup>S</sup> x C <sup>R</sup>	AC <sup>S</sup>	43	36
C <sup>R</sup> x A <sup>S</sup>	CA <sup>R</sup>	4	4
backcrosses			
AC <sup>S</sup> x A <sup>S</sup>	...	22	24
CA <sup>R</sup> x A <sup>S</sup>	...	25	6
*Strains		Superscripts	
A=A/Jax		S=Sensitive strain	
C=C57BL/6		R=Resistant strain	
		Spontaneous Incidence	
		A/Jax → 5%	
		C57BL/6 → 0.2%	

Modified after Smithberg.<sup>121</sup>



drawn from public sale in Sweden in 1961. However, subsequent investigation has proved that the drug does not cause human malformations.

A number of commonly used drugs have been shown to be teratogenic in animals.<sup>117</sup> These include the salicylates, various antihistamines and phenothiazines, and the adrenocorticosteroids. However, surprisingly few agents are known to be teratogenic in man. These include thalidomide, certain synthetic steroids (in particularly susceptible hosts) and various antimetabolic and anti-cancer agents.<sup>108</sup> Whether the failure to identify particular agents as being causative in birth defects is due to varying susceptibilities and possible genetic polymorphisms is not known. There is adequate precedent for this explanation—for example, the masculinization of the fetus which occurs only in certain individuals subsequent to the use of progestational steroids.<sup>118</sup> There is even a more remarkable example in the varying susceptibility of inbred strains of mice to the production of cleft palate by certain teratogens.<sup>119,120</sup> The incidence of cleft palate in mice exposed to cortisone or 6-aminonicotinamide varies with the genotype (Table 5). The data also suggest that the teratogenic action of either agent is dependent upon the maternal strain.<sup>121</sup> Although there are slight differences between strains, the palate in mice normally closes between day 14 and day 15. The maximal time at which cleft palate is produced by cortisone is at day 11½ to day 12½, and by 6-aminonicotinamide at day 13 to day 14. The teratogenic effect of 6-aminonicotinamide is reversed by niacin. Therefore, although the effect of both agents is modified similarly by the maternal genotype, there is a difference in the time of maximal effect of the two teratogens and a probable difference in the mechanism of teratogenicity of the steroid and the niacin antagonist.

This example from experimental teratology illustrates a number of problems implicit in clinical teratology. The teratogenic effect of the cortisone is not apparent from the known metabolic effects of the drug. There are pronounced differences between the strains of mice, and, indeed, there must be differences in the genetic susceptibility to teratogenic agents in man. We have learned to accept postnatal biologic variability, and prenatal variability must be similarly complex. Although the time of maximum susceptibility to the two agents differs, and apparently their teratologic mechan-

ism differs, the morphologic defects produced are indistinguishable. Finally, the presumed maternal effect upon the teratogenicity of the two agents may reflect differences in drug metabolism by the pregnant subject.

The agent which has been studied most extensively for teratogenic action is thalidomide. The clinical aspects of thalidomide embryopathy have been delineated by Lenz.<sup>122</sup> The remarkable features of thalidomide teratogenicity are that there is a very short period of susceptibility in man (thirty-fourth to the fiftieth day after the last menstrual period), the nature of the malformation is related to the time of administration within the susceptible period, and the human fetus is a particularly sensitive organism. This latter property prevented detection of the drug's teratogenicity before its use in man. Rat, hamster, mouse and chicken embryos are quite resistant to thalidomide. Other primates and the New Zealand rabbit have a similar sensitive period and develop similar abnormalities. Recently the mechanism of this species specificity has been investigated. Schumacher et al have found that the biologic half-life of thalidomide in rabbits and rats is nearly identical.<sup>123</sup> The rate of absorption of the drug from the alimentary tract differed between the two species, but the resistance of the rat to the teratogenic effect was also seen after intravenous administration. Indeed, the teratologic effects of thalidomide in rats were distinct from those in man and rabbits; the axial skeleton was primarily involved in rats. Keberle<sup>124</sup> believes that the reason for the species specificity may be differences in placental permeability. Although it is possible that there are species differences in the metabolic conversion of the agent, present evidence indicates that the teratologic action of thalidomide is due to the drug itself and not due to any of its metabolites. Williams and coworkers have demonstrated that the drug may act as an acylating agent and have suggested that the teratogenicity may result from the direct acylation of nucleic acids.<sup>125</sup> This hypothesis was tested by Bakay and Nyhan, who investigated the binding of thalidomide by various macromolecules in the fetal and maternal rat.<sup>126</sup> They demonstrated that most of the radioactive thalidomide was bound to soluble proteins and that there was no evidence of binding to either RNA or DNA. Unfortunately, these studies were not performed with a susceptible species.

## Extrinsic Influences on Chromosomes

Recently it has been recognized that there are compounds which may be teratogenic by a mechanism other than an effect on fetal metabolism.<sup>127</sup> These are drugs which enhance chromosomal breaks. Breakage of the chromosomes in gonadal cells may produce gametes with balanced and unbalanced chromosomal complements. The chromosomal imbalance will yield an abnormal or nonviable fetus. A balanced chromosomal complement may result in a phenotypically normal fetus. However, the offspring of this individual may be abnormal due to the probability that gametes with unbalanced chromosomal complements will be produced. Drugs which increase chromosomal breakage are called radiomimetic in that they produce similar types of chromosome abnormalities as ionizing radiation. Examples of such agents are mitomycin C, streptonigrin, cytosine arabinoside, caffeine and lysergic acid diethylamide (LSD).

There have been a great number of recent reports on the cytogenetic effects of LSD.<sup>48,49</sup> LSD does increase chromosomal breaks in leukocyte culture.<sup>128</sup> However, the effect may not be a direct action of the drug, as there is no quantitative relationship between the extent of chromosomal breakage and the level or length of exposure to the drug. The *in vitro* studies led to an examination of leukocytes derived from persons who had taken LSD, usually of illicit origin.<sup>129</sup> This complicates the interpretation of these studies, as the illicit agent may contain biologically significant contaminants. A higher proportion of leukocytes with abnormal chromosomes has been found in LSD users.<sup>130,131</sup> However, as in the *in vitro* studies, there is no relationship between total dose and the interval between the last dose and the proportion of abnormal cells. Hungerford et al administered chemically pure LSD to volunteers and found abnormalities in leukocyte chromosomes in three-quarters of the persons studied.<sup>132</sup> These studies of human leukocytes demonstrate the effects of the agent upon somatic cells. A study of gametes was performed in mice by Skakkebaek.<sup>133</sup> With a very high dose (about 500 times the equivalent dose in man), spermatocytes from treated animals showed a four-fold increase in chromosomal abnormalities.

The possible teratogenicity of LSD has received emphasis in recent months. Cohen et al, reporting on the *in utero* exposure of nine children to LSD,

found a significant increase in chromosomal breaks in their somatic cells, but there were no associated developmental abnormalities.<sup>134</sup> There have been several case reports associating maternal LSD ingestion with birth defects in an infant.<sup>135-138</sup> In a few of these cases limb defects were noted, although the extensive data necessary to establish a precise relationship between the time of administration and the type of defect was not reported. The reports of LSD teratogenicity in experimental animals are conflicting. Warkany and Takacs<sup>139</sup> found no evidence of teratogenicity in rats after the administration of LSD, whereas Alexander et al<sup>140</sup> found a maximal period of susceptibility at day 4 with resultant limb defects. A period of LSD sensitivity in mice at day 7 with resultant cerebral defects has been described.<sup>141</sup> Geber studied the teratologic effects of various psychotomimetic agents and presented evidence that mescaline, LSD and brom-LSD cause malformations in hamsters.<sup>142</sup> There was no dose or time relationship evident from this study. Since brom-LSD is not a hallucinogen, and in this study produced similar birth defects to its non-brominated analogue, the psychotomimetic effect of the drug is probably unrelated to its teratologic effect, at least in the experimental animal.

There have been recent reports that a number of agents, including the widely used artificial sweetener sodium cyclamate,<sup>50</sup> enhance the production of chromosomal breaks in cultured cells. It remains to be determined whether these agents which accelerate chromosomal breakage *in vitro* are injurious to gametes and whether they are teratogenic. This area has been recently discussed by German<sup>143</sup> and by de Grouchy.<sup>144</sup> It is apparent that our knowledge of the developmental consequences of chromosomal breakage must be further elucidated.

From the foregoing discussion it should be clear that in man it may be difficult deciding whether a drug is teratogenic or whether a particular malformation is drug-related. One approach to this problem is developing accurate, predictive, drug testing procedures. A World Health Organization scientific group met in November of 1966 to examine the problem of testing of drugs for teratogenicity. The group recommended a number of procedures for teratologic screening and made recommendations to enhance the predictive value of animal screening.<sup>145</sup> In December of 1966, the Food and Drug Administration established the



TABLE 6.—*Some Diseases in Which Fibroblast Cultures Demonstrate Metachromasia*

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Cystic fibrosis
Fabry's disease
Familial hyperuricemia
Familial amaurotic idiocy
Gaucher's disease
Generalized gangliosidosis
Hunter's syndrome
Hurler's syndrome
Marfan's syndrome
Pompe's disease
Pseudoxanthoma elasticum

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Adverse Reaction Task Force within its Bureau of Medicine. The role of this unit was to establish better reporting procedures, investigate reports of adverse drug effects and communicate new information to physicians.<sup>146</sup>

It is important to note that although animal testing may be expensive, proof that a drug is a teratogen in man cannot be obtained from animal studies. Nonetheless, new labeling regulations for drugs have been established on the basis of animal testing.<sup>147</sup> If the animal data on the teratogenicity of a drug contains nothing significantly unfavorable, then the package insert must bear the statement that "safety in pregnancy has not been established and the use in pregnancy is not recommended." If the animal data contains unfavorable results and there is no human experience to contradict or make a safety determination, then the drug must be labeled as "contraindicated in pregnancy." The Food and Drug Administration requires safety information on the use of the drugs in pregnant women, particularly in the first trimester, as a prerequisite to removing these precautionary statements. It should be noted that if these precautions had been enforced at the time that salicylates or antihistamines were introduced, and there was no human experience to contradict the animal evidence, these two classes of drugs would be labeled as contraindicated in pregnancy.

### Cell Culture as a Diagnostic Tool

Considerable advances have been made in recent years in delineating the biochemical phenotype of inherited disorders. In addition to classical means of examining body fluids (urine, plasma) considerable knowledge has been gained by examination of the cellular components of blood and, most recently, by the utilization of monolayer tissue culture. The use of cellular components to define

disorders of aberrant metabolism has enabled investigators to accurately establish the enzyme(s) involved, rather than deduce the abnormality from the accumulation of a precursor or the lack of an appropriate product. The use of tissue culture as a diagnostic tool has also allowed the direct examination of chromosomes from tissues other than leukocytes and, as will be discussed below, has provided a technique whereby fetal cells may be studied.

Due to technologic advances in tissue culture, skin fibroblast cultures have become readily available. Although it had been assumed that fibroblasts were relatively undifferentiated and therefore lacked enzymes of a specialized nature, a number of instances have been described recently in which fibroblast cultures have led to the identification of abnormal molecular processes.<sup>148</sup> Fibroblasts are easily obtained from a tiny biopsy specimen of skin. These are readily cultured, and, with time, sufficient cells for cytogenetic, microscopic and biochemical analysis become available. A great number of enzyme deficiency states have been detected in fibroblast cultures.<sup>149</sup>

Acid mucopolysaccharides are made by fibroblasts and they are easily identified by the use of organic dyes which stain these compounds metachromatically. Thus, the evaluation of mucopolysaccharide accumulation was one of the initial instances in which this technique was used. Since the observations of Danes and Bearn on mucopolysaccharide storage diseases,<sup>150</sup> a large number of reports have appeared in which fibroblast cultures and cellular metachromasia have been used to characterize other diseases. Table 6 is a partial list of these diseases. Detection of metachromatic staining in fibroblast cultures is quite simple and the technique has recently been extended to cultured leukocytes.<sup>151</sup> Metachromatic staining, however, is not specific for any compound. Any macromolecule which is a polyanion may be stained with an appropriate cationic dye and give a metachromatic reaction.<sup>152</sup> A positive staining reaction is not diagnostic, as can be seen from the partial list of diseases in which cellular metachromasia has been described. Most of these diseases are inherited as autosomal recessive traits and in many of the studies both parents also show similar metachromatic granules in cultured fibroblasts. Consequently, the method may not distinguish between the homozygous and the heterozygous state.



Cellular metachromasia has been described in cystic fibrosis of the pancreas,<sup>153</sup> the commonest autosomal recessive illness occurring in whites with the incidence of the heterozygous carrier estimated to be one in 20 to 25 individuals. Cultured fibroblasts derived from patients and their parents are reported to contain metachromatic granules in one of three apparently genetically determined distributions. The recent data of Nadler,<sup>154</sup> however, indicate that metachromatic granules in cultivated fibroblasts is not a consistent finding in patients with cystic fibrosis.

Metachromatic staining may vary with the conditions of tissue culture, including the type of medium, the length of time in culture, and the number of subcultures. Recently, it was shown that metachromasia is demonstrable in cultured fibroblasts from skin biopsy specimens of 27 percent of pediatric patients with a variety of diagnoses, including Down's syndrome, Turner's syndrome, Wilson's disease and multiple congenital anomalies.<sup>155</sup> Nadler reported that approximately 15 percent of all cell lines in his laboratory stain metachromatically.<sup>154</sup> These incidences of metachromasia are probably not accountable by the combined heterozygous frequency of disease incidences for illnesses known to be associated with metachromasia. Thus, the presence of metachromatic granules in cultured fibroblasts is a widespread phenomenon which occurs in a variety of situations not thought to be associated with mucopolysaccharide abnormalities. In short, metachromatic staining of fibroblast cultures does not appear to be a useful technique to support clinical diagnoses or to identify the carriers of specific genes, nor can it be reliably used to determine the phenotypic status of the fetus.

The presence of metachromatic granules in Hurler's disease<sup>150</sup> and Marfan's disease<sup>156</sup> are related to the specific accumulation of dermatan sulfate<sup>157</sup> and hyaluronic acid respectively. However, a recent report by Matalon, et al on metachromatically-staining skin fibroblasts from a patient with Fabry's disease<sup>158</sup> reveals that, in addition to an accumulation of a specific glycolipid, the cells had an increased content, but a normal distribution, of mucopolysaccharides. While glycolipids and mucopolysaccharides may share the same degradative enzymes, resulting in accumulation of both metabolites, available evidence suggests that these enzymes are highly specific.<sup>159</sup> The authors infer that the apparently nonspecific nature of muco-

polysaccharide accumulation, as reflected by metachromatic staining, may arise as a general and secondary consequence of cell membrane abnormality. Experimental evidence is lacking for this hypothesis, but it is more reasonable than assuming that metachromatic granules reflect considerable hitherto unrecognized biochemical heterogeneity in genetic disorders.

## Prenatal Diagnosis

Considerable interest recently has been devoted to means of detecting fetal abnormalities *in utero*. The use of transabdominal amniocentesis for the detection and management of Rh-isoimmunization<sup>63</sup> provided ample evidence that this technique could be utilized for ascertainment of other aspects of fetal physiology and metabolism. The technique of transabdominal amniocentesis, although potentially dangerous to fetus as well as the mother, has proved to be relatively safe in experienced hands.<sup>149</sup> For prenatal diagnosis, the optimal time for this procedure appears to be at approximately 12 to 16 weeks of fetal gestation. The material obtained is predominantly amniotic fluid, but contains a complement of cells. Removal of 10 ml of fluid is adequate for an appropriate examination. Although examination of the fluid has been very helpful in the management of Rh-isoimmunization, relatively few studies have been performed on use of the fluid for prenatal detection of hereditary disease. Since amniotic fluid is derived in part from fetal urine, it is probable that altered concentrations of various urinary metabolites could be readily assessed in the fluid, as suggested by recent studies.<sup>160-162</sup>

The cellular component of amniotic fluid has been the primary focus of recent investigation. Analysis of the cells for sex chromatin is relatively easy. This means of determination of the fetal sex has been reported to be useful in management of pregnancies in women who are carriers of x-linked recessive disorders.<sup>149</sup> Obviously, determination of the fetal sex in such circumstances (for example, hemophilia, muscular dystrophy) does not establish the diagnosis in the fetus. Amniotic fluid cells have been examined directly for the presence of particular enzymes.<sup>163</sup> The source and physiologic features of these cells are subjects for necessary investigation.<sup>164</sup>

Recently several groups have investigated the cultivation of amniotic fluid cells.<sup>152,167,168</sup> The cell cultures have been utilized for karyotypic

analysis and the intrauterine diagnosis of chromosomal abnormalities have been reported.<sup>165,167-169</sup> Assessments of the chromosomal status of the fetus have been made in several instances where the parent is a known translocation carrier.<sup>149,165</sup> Nadler is making fetal chromosome analysis available to pregnant women after the age of 40 years. While the risk of chromosomal abnormality in this group of women is low (2 to 4 percent), the procedure is more than justified considering the low morbidity from amniocentesis performed by an experienced physician.

Biochemical studies of cultivated amniotic fluid cells have been performed by a number of groups (see reference 149 for review). Enzymatic studies of such cells have allowed the intrauterine detection of galactosemia, Pompe's disease, deficiency of lysosomal acid phosphatase, mucopolysaccharidoses, Lesch-Nyhan syndrome and other inborn errors of metabolism. The ability to detect various genetic disorders *in utero* is an outstanding achievement, although the method is limited to relatively few centers at present. It will become more readily available and should provide populations at risk (known heterozygotes) with precise information on the status of the intrauterine organism. The legal question of the interruption of pregnancy should be readily resolved in the near future.<sup>170</sup> Recent experience has indicated that legislatures will allow the interruption of pregnancy to prevent the birth of an infant with a severely disabling disorder.<sup>171</sup>

Less easily resolved may be the scientific problems inherent in the technique. The time of amniocentesis is an important factor in determining whether a prenatal diagnosis may be made. In certain instances, sufficient quantities of cultured cells became available for enzymatic assay too late for intrauterine diagnosis or for therapeutic abortion (see, for example, reference 172). With the utilization of microtechniques for enzymatic assay and greater experience with amniocentesis at earlier stages of pregnancy, the time factor can become inconsequential. Of greater importance is the precise identification of the biochemical phenotype of a particular disorder. For example, a decrease in the amount of  $\beta$ -galactosidase has been described in generalized gangliosidosis.<sup>173</sup> However, a similar decrease in this enzyme has been described in Hunter's syndrome.<sup>174</sup> Consequently, documentation of depressed enzyme levels in amniotic fluid cell cultures would not be diagnostic.

The question also arises as to whether the cultured cell normally expresses the gene for the enzyme under investigation. For example, glucose 6-phosphatase is present only in liver and kidney cells.<sup>175</sup> Consequently, this probably precludes detection of Von Gierke's disease in the fetus by analysis of amniotic fluid cells. Another problem inherent in the utilization of amniotic fluid cell cultures is the normal time of appearance of the enzyme in the fetus. The fetus is qualitatively distinct enzymatically from the mature organism and, therefore, the absence of the enzyme in fetal tissue may not mean a deficiency of the enzyme. For example, phenylalanine hydroxylase does not appear in the liver until after birth.<sup>176</sup>

A possible example of these difficulties has been noted by Nadler et al.<sup>156</sup> These investigators report that cultivated amniotic fluid cells failed to demonstrate metachromatic granules in a child born to known heterozygotes for cystic fibrosis. The child was born with classic cystic fibrosis, including meconium ileus and a positive sweat test. Cultivated fibroblasts, derived from the child during the neonatal period, contained metachromatic granules. It is possible in this instance that whatever is responsible for the metachromasia either did not appear until postnatal life or is not capable of being demonstrated in the amniotic fluid cell cultures in this disease. It is clear that the presence or absence of metachromasia cannot be reliably used to determine the intrauterine status of the fetus.

The technique of intrauterine diagnosis is unique in medicine. Here, one is attempting to make a diagnosis in an individual on the basis of laboratory results and family history and without recourse to the usual modes of diagnosis. At present we are unable to "examine" the fetus to visualize the individual with the abnormal phenotype. Consequently, there must be a precise relationship between the abnormal laboratory results and the phenotype. Although there have been a number of enzymes demonstrated in cultured amniotic fluid cells,<sup>164</sup> not all of these are associated with diseases at the present time. Similarly, a number of abnormalities of karyotypes have recently been found which are apparently unrelated to the phenotypic abnormality.<sup>55</sup> The recently recognized variations in intrapair chromosomal morphologic features might appear to be due to an unbalanced translocation.<sup>177</sup> Certainly, great scrutiny will be required before antenatal diagnosis becomes a routine pro-



cedure. Nevertheless, the technique is without question the most significant advance in birth defects research of the past few years.

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## DECOMPRESSION AFTER COLON ANASTOMOSIS

"Decompression of the proximal colon following colon anastomosis is generally felt to be of value in decreasing anastomotic complications. . . .

"We feel that the indwelling rectal tube [passed up through and above the anastomosis] provides adequate decompression of the proximal colon. We've also found that it decreases the need for nasogastric suction. We don't employ the rectal tube routinely, but only if there's undue distention, nausea, etc.; and almost 20 percent of our patients do subsequently have to have a Levin tube passed. It insures a patent anastomosis and allows reinforcement and removal of tension without any fear of angulation or of compromising the size of the lumen. It also serves as a route for the administration of local antibiotics. [One surgeon] has even advocated putting a polyethylene catheter into the colon and bringing it out through the abdominal wall just for this purpose—bathing the anastomotic site with antibiotics. All in all we feel the indwelling rectal tube leads to fewer anastomotic complications."

—WILLIAM R. C. STEWART, M.D., Columbus  
Extracted from *Audio-Digest Surgery*, Vol. 15,  
No. 23, in the Audio-Digest Foundation's subscription series of tape-recorded programs.



## MEDICAL STAFF CONFERENCE

### "Shock Lung"

*These discussions are selected from the weekly staff conferences in the Department of Medicine, University of California Medical Center, San Francisco. Taken from transcriptions, they are prepared by Drs. Martin J. Cline and Hibbard E. Williams, Associate Professors of Medicine, under the direction of Dr. Lloyd H. Smith, Jr., Professor of Medicine and Chairman of the Department of Medicine.*

DR. SMITH:\* The case summary this morning will be given by David Lehman, a fourth-year clinical clerk on our service.

MR. LEHMAN:† A 17-year-old girl was admitted with multiple fractures and in shock to Woodland Memorial Hospital. The left subclavian artery had been torn and the spleen had been lacerated. The artery was repaired and the spleen removed. However, during the operative procedure there was massive abdominal bleeding and for 15 minutes the blood pressure was not measurable. The patient was transfused with 12 liters of fluid, and frank pulmonary edema with pink, frothy sputum developed. The edema was corrected by phlebotomy. Tracheostomy was performed, and the patient was placed on a volume respirator. Despite an inspired oxygen concentration of about 50 percent, the arterial oxygen tension was only 40 to 60 mm of mercury (mmHg).

The patient had postoperative fever and a firm abdomen, and a second laparotomy was performed ten days after the first. No abscess was found. Chest tubes had to be inserted bilaterally because pneumothoraces repeatedly developed. At this time high doses of steroids were begun to retard pulmonary fibrosis. On 9 September an attempt

was made to transfer the patient to a Bird respirator, but the maneuver was accompanied by two episodes of bradycardia, coma, and dilated pupils which lasted several hours.

The patient's course was also complicated by pulmonary infections. *Enterobacteriaceae* were grown from the tracheal aspirate, left empyema developed, and *Pseudomonas* were repeatedly grown from material taken from the left chest tube. She was treated at various times with cephaloridine (Loridine®), gentamicin (Garamycin®), and colistin (Coly-Mycin®). Although she had persistent vomiting and diarrhea, an upper gastrointestinal series showed no evidence of obstruction.

After 16 September the patient was successfully maintained with a Bird respirator. However, an attempt at spontaneous ventilation, using 100 percent oxygen, resulted in carbon dioxide narcosis, an arterial oxygen tension of 106 mmHg, and a carbon dioxide tension of 100 mmHg. As it was impossible to discontinue use of the Bird respirator, the patient was transferred to this hospital 6 October 1969.

On physical examination she appeared chronically ill, but alert and not in acute distress. The pulse was 130 per minute and regular, blood pressure was 140/80 mmHg, respirations were 32 per minute, and temperature was 39.7°C. Significant abnormalities were a left-sided Horner's syndrome;

\*Lloyd H. Smith, Jr., M.D., Professor and Chairman, Department of Medicine.

†David Lehman, fourth-year medical student.



bilateral chest tubes which drained only serous fluid; dullness over the entire chest except for hyperresonance at the left base; decreased breath sounds; diffuse, crackling rales; and tubular breath sounds at the left base. Cardiac examination was normal. The abdomen had a well-healed, left subcostal surgical scar and was soft and distended. The liver could be felt 10 cm below the costal margin and was firm and nontender. Neurologic examination revealed pronounced muscle wasting and weakness.

Laboratory data included the following: hematocrit, 35 percent; leukocyte count, 22,500 per cu mm; urinalysis, 2+ protein, 15 to 20 white cells, and many bacteria in every high power field; blood urea nitrogen and creatinine, normal. Liver function tests showed a normal bilirubin, a serum glutamic oxaloacetic transaminase (SGOT) of 81 units, and alkaline phosphatase elevated to 187 (upper limit of normal, 80). Blood gases and pH on admission, at an inspired oxygen level of 92 percent, were: Oxygen partial pressure, 106 mmHg; carbon dioxide partial pressure, 65 mmHg; pH, 7.38. The tidal volume measured 850 ml, of which 78 percent was calculated as wasted ventilation (dead space).

The patient continued to be febrile. *Enterobacteriaceae* and *Herellea* organisms were grown from a tracheal aspirate, and she was treated with chloramphenicol (Chloromycetin®) and kanamycin (Kantrex®). All other cultures, including blood, tube drainage and urine, were negative. The arterial blood gas levels became progressively worse, and on 14 October, at an inspired oxygen level of 92 percent, the oxygen tension was 56 mmHg, carbon dioxide tension was 67 mmHg, and the pH was 7.42. The next day, despite the administration of 100 percent oxygen, the oxygen tension was only 46 mmHg, the carbon dioxide tension was 72 mmHg, and the pH was 7.42. On 16 October, after several episodes of bradycardia, the patient died.

DR. SMITH: Thank you very much. We are fortunate to have John Murray here to open our discussion. Dr. Murray, what is "shock lung," how do we make this diagnosis, and what is known about its pathogenesis? Is there anything else we should have tried to save this young girl?

DR. MURRAY: \* I will try to answer each of those

TABLE 1.—Clinical Features of "Shock Lung"

Progressive dyspnea
Progressive hypoxia
Hypotension from any cause
12 to 24 hour latent period
Increasing ventilator pressure
Progressive infiltration on x-ray

questions. The young woman described today presents most of the clinical features of what is now called "shock lung." Shock lung has evoked a good deal of recent interest because of the large number of battle casualties from Vietnam who have exhibited this syndrome<sup>1</sup>; in fact, in military circles the condition is known as "DaNang lung." The recognition of shock lung is increasing because of the rapid evacuation to medical facilities of individuals who are wounded on the battlefield or who are seriously injured in civilian life. Resuscitative measures can be applied rapidly so that life is prolonged and the more latent and insidious manifestations of respiratory insufficiency have time to develop.

Bredenberg's experience with 27 patients having various forms of shock presents some idea of the magnitude of the problem of shock lung<sup>2</sup>: Six of nine patients who died acutely in the throes of hemodynamic crisis had severe pulmonary problems, manifested both clinically and pathologically. It was thought that respiratory insufficiency was a major factor contributing to the death of these six patients. More relevant to the case under discussion today was Bredenberg's belief that respiratory insufficiency was also the primary cause of six of eight "late deaths" (deaths occurring after resuscitation from the shock episode). Bredenberg was able to correlate both prognosis and mortality of his patients with estimates of the severity of pulmonary involvement.

Shock lung is difficult to define, but Table 1 summarizes the typical clinical features of the syndrome. Shock lung can follow hypotension from any cause: severe trauma, surgical procedures, bleeding, burns, infection, others. Although pulmonary manifestations may appear during the acute hemodynamic crisis, more commonly there is a latent period of 12 to 24 hours (occasionally longer) during which respiratory abnormalities are minimal or nonexistent. If the patient is alert and conscious after the 12- to 24-hour interval, he will begin to complain of progressive shortness of breath, and arterial blood studies will reveal a progressive fall of arterial oxygen tension. Patients

\*John F. Murray, M.D., Professor of Medicine.

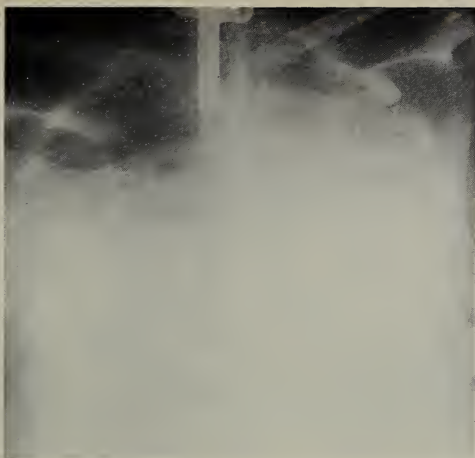


Figure 1.—Chest x-ray of a patient taken 24 hours after a prolonged hypotensive episode from retroperitoneal hemorrhage. Note patchy, irregular pulmonary infiltrations.

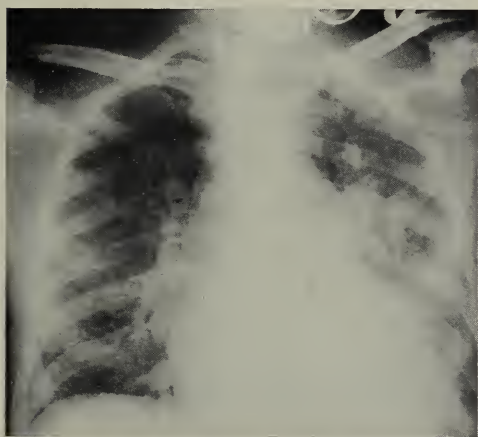


Figure 2.—Chest x-ray of same patient shown in Figure 1 taken four days after hemorrhage occurred. The infiltrations are more extensive and nearly confluent.

who are receiving assisted ventilation will require increased inspiratory pressure to maintain arterial blood gas tensions. If serial radiological examinations are being carried out, pulmonary infiltrations will show an increase.

Figure 1 shows an x-ray film of the chest, taken 24 hours after admission, of a patient who entered San Francisco General Hospital following severe multiple traumatic injuries. The film shows multiple, patchy, irregular infiltrations. The infiltration may begin to clear at this time, but often the con-

TABLE 2.—Factors Contributing to "Shock Lung"

<i>Intrinsic</i>
Toxins
Microemboli
Myocardial failure
Vasoactive substances
<i>Extrinsic</i>
Infection
Overhydration
Oxygen, drugs, etc.

dition worsens. A more advanced phase of illness, with extensive, multiple and nearly confluent infiltrations throughout both lung fields, is illustrated in Figure 2.

The pathological findings in this condition have been quite consistent, regardless of the cause of shock. Gross lung specimens are usually intensely hemorrhagic, congested and airless, and they sink rapidly when put in fluid. The cut surface of the lung is nearly always described as resembling liver. In microscopic sections one sees intense vascular congestion, and usually the interstitial and alveolar spaces are filled with extravasated fluid and blood. In some parts of the lung hyaline membranes may be found, while in other areas there may be evidence of pulmonary infarction with necrosis and hemorrhage.

In my opinion the reasons for the profound clinical and pathological disturbance in shock lung are multiple. It is virtually impossible to single out any one factor as being responsible. I have divided factors contributing to shock lung into intrinsic and extrinsic causes (Table 2). By "intrinsic" I mean those causes that are inherent consequences of the pathophysiology of the underlying condition causing the shock. "Extrinsic" refers to those causes that are not part of the primary disease but which develop or are externally introduced (often inadvertently) by the physician's intervention.

### Intrinsic Factors

Several toxins are known to be elaborated in processes associated with shock. In addition to endotoxins from bacterial infection, toxins from the ingestion of chemical substances or the inhalation of noxious gases may be a factor. It is also thought that endogenous toxic substances may be absorbed from the gut or possibly released from devitalized or ischemic tissues in many hypotensive states.

Many vasoactive substances are also known to exert profound effects upon the lung: Catechola-

mines, histamine, bradykinin and angiotensin, among others, may be released from either cellular constituents of blood or lung tissue itself. In addition, it is now recognized that a number of polypeptides produced in the conversion of fibrinogen to fibrin have profound vasoactive effects on pulmonary vessels and may contribute to the development of abnormal pulmonary function.

A number of factors associated with shock can induce intravascular coagulation. Microemboli are thought by some investigators to play a very important role in the pathogenesis of shock lung. Not only microemboli of platelet and fibrin aggregates, fat, and other tissue elements, but also macroemboli in the usual form of venous clots can contribute to the development of this syndrome. Myocardial failure was previously thought to play an important role in the production of shock lung but now is thought to be unimportant in the genesis of pulmonary failure associated with hemorrhage, extensive trauma or endotoxin shock. Undoubtedly cardiac failure is a significant factor in pulmonary involvement secondary to myocardial infarction and probably in pulmonary disorders resulting from an overdose of barbiturates and other drugs which are known to depress myocardial function.

### Extrinsic Factors

An extremely important extrinsic cause of shock lung is overhydration; in fact, there are many experts in the field who think that overhydration is the single most important, if not the sole cause of shock lung. The recent emphasis in the emergency treatment of shock, both on the battlefield and in the emergency room, is on the massive and swift replacement of intravenous fluids. In some instances patients have received literally gallons of fluid within a 12- to 24-hour period.

The toxic effects of oxygen have also been incriminated as a cause of this syndrome, largely because in experimental animals oxygen administered in high concentrations for prolonged periods produces a reaction in lung tissue very similar histologically to that seen in shock lung. Moreover, most patients in shock are given high concentrations of oxygen for long periods, as was the patient under discussion today.

Finally, pulmonary infections must be considered as contributing to the production of shock lung. The patient's pulmonary clearance mechanisms are often substantially impaired, the upper

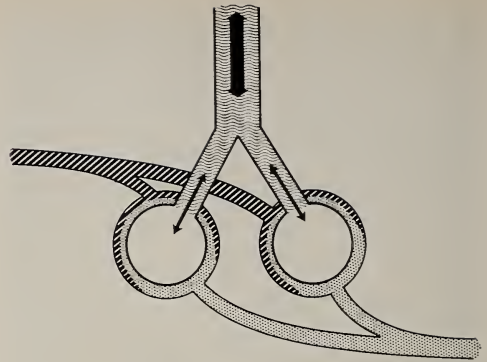


Chart 1.—Schematic representation of a normal lung showing proportionately distributed inspired air and pulmonary capillary blood flow. (After Comroe and coworkers.<sup>2</sup>)

airway is frequently bypassed, suction catheters are introduced into the tracheobronchial tree, and mechanical ventilators are often used. All of these measures serve to introduce and promote the development of infection.

Regardless of whether single or multiple mechanisms are operating in shock, the sites of involvement appear to be in small pulmonary blood vessels and the alveolar capillary membrane, where profound alterations in hydrostatic forces and vascular permeability take place. Microemboli, for example, plug pulmonary arterioles and tend to raise pulmonary arterial pressure. It is difficult to account for the extravasation of blood from an obstruction to the pulmonary arteriole, but leakage could occur after retrograde filling through the pulmonary veins or from collateral blood flow in the bronchial circulation. Many of the vasoactive substances that I mentioned are thought to affect pulmonary venules and could possibly cause capillary congestion and interstitial and alveolar hemorrhage. Undoubtedly, an important factor in the development of the pathological lesion is the pronounced alteration in the vascular permeability of the alveolar-capillary membrane, with the consequence that both plasma constituents and erythrocytes escape into the interstitial space and ultimately into the alveoli and airways.

Pathophysiological disturbances may cause significant changes in pulmonary gas exchange. Chart 1 presents an idealized lung in which ventilation is uniform: Every breath of air is distributed evenly through the airways to the alveoli. Similarly, there is uniform blood flow — incoming, mixed



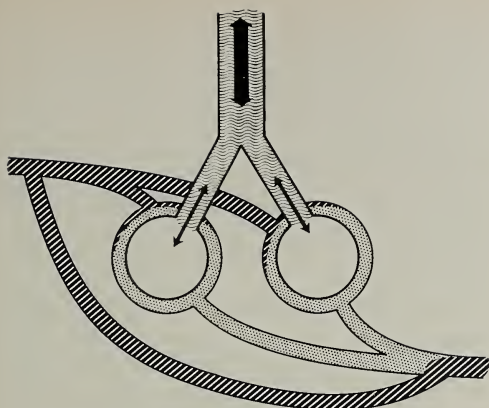


Chart 2.—Schematic representation of a lung showing a large right-to-left shunt.

venous blood is also distributed evenly to the alveoli. Each alveolus, therefore, receives a proportionate share of blood and fresh air. When blood flow and ventilation are equally matched in this fashion, there is optimum uptake of oxygen and release of carbon dioxide.

In shock lung disturbances occur in the matching of inspired air with incoming blood and lead to abnormalities of arterial blood gases and the total volume breathed per minute. Chart 2 demonstrates schematically the major problem that occurs in the arterialization of blood in this condition—the development of a right-to-left shunt. Thus a pathway exists for mixed venous, or unsaturated blood, to bypass alveoli completely, so there is no contact with inspired air. The unsaturated blood traverses the lungs to the arterial side of the circulation, where it causes a pronounced reduction in arterial oxygen tension. In the 27 patients studied by Bredenberg<sup>2</sup> the average shunt was 42 percent of the output of the right heart. In two of the individuals 80 percent of the total cardiac output was shunted.

From a clinical point of view, right-to-left shunting causes hypoxia that is difficult to correct by administration of oxygen. A poor response is implicit in the diagram shown in Chart 2 because in this condition a pathway always exists through which unsaturated blood can bypass ventilated alveoli. Neither patent foramen ovale, arteriovenous fistulas, nor other large anatomical shunts have been identified in patients dying from shock lung. Thus we infer from this observation that shunting of blood takes place through areas of atelectasis,

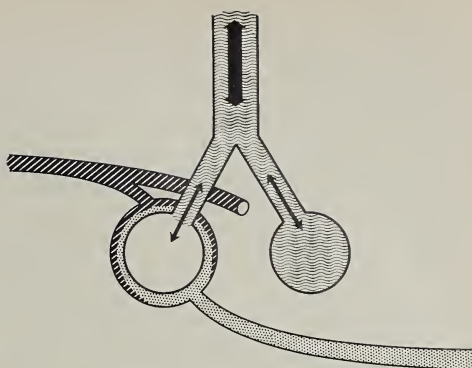


Chart 3.—Schematic representation of a lung showing excessive wasted ventilation.

through alveoli that are filled with fluid, or through zones of pneumonia, all of which serve as sites where there is no ventilation but where blood flow is maintained. A right-to-left shunt can also be regarded as wasted blood flow because a fraction of the output of the right heart is “wasted” in terms of its potential contribution to gas exchange.

Not only is blood flow wasted in shock lung but so is ventilation. Chart 3, a schematic model of wasted ventilation, displays a lung unit to which there is no blood flow. The air that ventilates the unit cannot participate in carbon dioxide release or oxygen uptake because of the absence of blood flow in the pulmonary capillaries. In many patients in shock, the amount of wasted ventilation is often above 50 percent of each breath and may reach 75 to 80 percent, as in the patient today who had a wasted ventilation of 78 percent. In the early stages of shock lung, patients are usually able to maintain normal or low arterial carbon dioxide tensions despite an increase in wasted ventilation. This maintenance can only be achieved by an increase in minute volume of respiration even greater than in wasted ventilation, and the patients tend to breathe rapidly and very deeply. In any given period of time they breathe large volumes of air, but much of it does not participate in gas exchange. As the severity of shock lung increases, arterial carbon dioxide tends to rise. The accumulation occurs because dead space increases to an even greater amount and the mechanical properties of the lung become so impaired that high levels of ventilation can no longer be maintained. Hence the discovery of an elevation of carbon dioxide tension in the patient's arterial blood is an ominous prognostic finding.

TABLE 3.—*Treatment of "Shock Lung"*

Specific Treatment Underlying Condition
Volume replacement
Vasoactive drugs
Antibiotics
Oxygen (tension of 80 to 100 mmHg)
Ventilatory Support
Maintain carbon dioxide tension of 40 to 45 mmHg
Deep breath every 10 to 15 minutes
Diuretics
?Heparin

TABLE 4.—*Determination of Adequacy of Hydration*

Measure urine output
Measure blood pressure
Weigh patient carefully and often
Measurements of central venous pressure inadequate
Measurements of pulmonary arterial pressure necessary
Adequate humidification = no insensible loss

Table 3 shows some aspects of treatment directed toward overcoming and possibly preventing some of the features of shock lung. I will not dwell on the specific treatment of the underlying condition, since this obviously depends on the cause of shock.

## Hydration

Several features should be considered when trying to determine the adequacy of hydration in these patients (Table 4). Systemic arterial blood pressure and urine output are reliable indicators of the adequacy of perfusion of the systemic vascular bed, so that measurements of arterial pressure and urine volume should be obtained frequently. The patient also should be weighed carefully and often, but in many individuals with multiple traumatic injuries, there may be extravasation and sequestration of large volumes of fluid in body compartments. Thus the patient may have considerable weight gain which does not necessarily reflect an adequate intravascular volume.

A mistake that is quite commonly made is to believe that a patient with a normal central venous pressure can always tolerate additional intravenous fluid. We have had several patients go into severe pulmonary edema from overhydration even though the central venous pressures were perfectly normal. This condition can be explained by considering the hemodynamic factors that control fluid movement in the lungs. A better measure of the hydrostatic forces that promote extravasation into the lung is pulmonary arterial pressure, which is

much more useful than central venous measurements in the management of patients with complicated hypovolemic disorders. Unfortunately, we cannot rely solely on normal pulmonary arterial pressure values to exclude the possibility of excessive fluid formation in the lungs. Dr. Norman Staub<sup>4</sup> of the Cardiovascular Institute has shown that pulmonary arterial pressure may change only slightly in pulmonary edema that results from changes in the permeability of the alveolar capillary membrane. Therefore, pulmonary arterial measurements indicate only those causes of pulmonary edema that are associated with elevated pressures in the precapillary and pulmonary arterial bed. However, in trying to settle the very difficult problem of fluid replacement in persons with multiple traumatic injuries or hypovolemia from other causes, measurements of pulmonary arterial pressure are probably the best indicators available today of the adequacy of fluid replacement.

Calculations of fluid balance usually include insensible water losses. This does not apply if the patient is on a mechanical respirator and is receiving adequate mainstream humidification (as he should), for then no insensible fluid loss occurs. If overhydration occurs, relief may be obtained by the judicious use of diuretics.

## Use of Oxygen

There is increasing evidence that the administration of high concentrations of oxygen (80 to 100 percent) for four to six days injures the alveolar capillary membrane and may cause severe pathological disturbances.<sup>5</sup> Since patients with shock lung often require oxygen in high concentrations for long periods, it has been speculated that oxygen toxicity may compound and perpetuate the pulmonary disorder. In order to minimize the risk of oxygen toxicity, the patient should be given the lowest concentration of oxygen necessary to produce an adequate amount of oxygen in the arterial blood stream. As one can observe from the oxyhemoglobin dissociation curve (Chart 4), when the oxygen tension is about 60 mmHg, the patient's hemoglobin is about 90 percent saturated. Increasing the pressure above 60 mmHg adds very little oxygen to the circulating blood stream. Therefore, we recommend that the arterial oxygen tension be maintained around 80 mmHg and not raised above 100 mmHg. This maintenance can be achieved by driving respirators from compressed air sources and supplementing the patient's in-

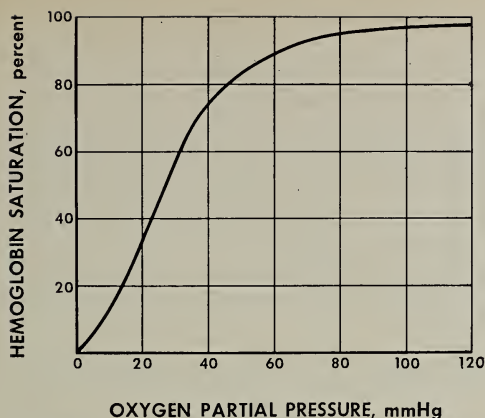


Chart 4.—Oxyhemoglobin dissociation curve for human blood at pH 7.40 and temperature 37°C.

spired airstream with only enough oxygen to reach the desired arterial oxygen concentration.

In this medical center Dr. F. William Blaisdell has been trying to define the contribution of disseminated intravascular coagulation to the pathological abnormalities of shock lung. He believes that coagulation is extremely important and may play a central role in the development of the pulmonary lesions seen after vascular operations.<sup>6</sup> Intravascular coagulation can be induced by many of the factors present in shock (Chart 5) and can be prevented by the use of heparin. Since many patients who are candidates for shock lung have had extensive tissue trauma and bleeding episodes, the use of heparin is a difficult and controversial decision. We have recently collaborated with Dr. Blaisdell and Dr. Stallone<sup>7</sup> in a series of experiments designed to study the problem. We hope that the results of these experiments will help us avoid the administration of heparin by providing another method of preventing pulmonary damage despite the presence of widespread intravascular clotting.

## Ventilation

We placed clamps on the abdominal aortas of anesthetized spontaneously breathing dogs for four hours to cause the lower extremities to become ischemic. When the clamps were removed and blood flow restored, sequestered blood and metabolic products were flushed out of the dogs' legs, through the venous circulation, and into the lungs. Half the animals died and postmortem examination showed intensely congested lungs with patchy areas

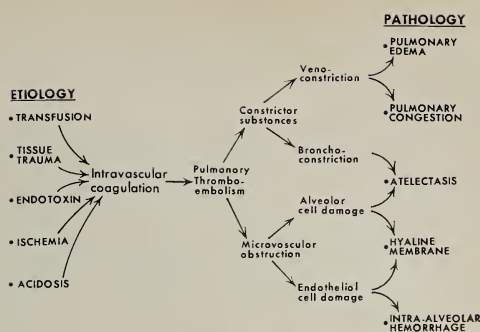


Chart 5.—Diagram showing how intravascular coagulation can be initiated by many factors associated with shock. How coagulation, in turn, can produce many of the pathological features of "shock lung." (From Stallone and coworkers.)

of pulmonary infarction. Microscopic lung sections showed interstitial and alveolar hemorrhage, alveolar fluid accumulation, and perivascular hemorrhage with emboli in small arteries and capillaries. These findings are quite similar to those seen in shock in man. A second group of anesthetized animals also had clamps applied to the aortas for 4 hours, but in addition these dogs were ventilated with a volume respirator that periodically hyperinflated the lungs at 10-minute intervals. The lungs were grossly normal, and microscopic sections failed to show interstitial or alveolar hemorrhage, even though the typical findings of platelet and fibrin aggregates in small pulmonary blood vessels were present.

These data indicated to us that atelectasis is crucial to the evolution of shock lung. If atelectasis can be prevented by maintaining adequate volumes of ventilation and by artificially hyperinflating the patient every 10 to 15 minutes, the usual sequence of events can be interrupted.

## Summary

We can draw the following conclusions about shock lung:

- Respiratory failure is a frequent and important accompaniment of shock and can occur regardless of the cause of the patient's condition.
- The clinical constellation constitutes a syndrome to which multiple factors undoubtedly contribute.
- The major physiological abnormalities are (1) a pronounced reduction in arterial oxygen tension from a large, physiological, right-to-left shunt;



(2) a striking increase in the patient's wasted ventilation; and (3) a pronounced alteration of mechanical properties that affect the patient's ability to ventilate.

• Adequate treatment requires an understanding of the pathophysiological disturbances that take place in shock. Attention is required to prevent some of the complications that may arise through injudicious therapy. I would like to emphasize that, although as yet unproven by adequate clinical trials, early assisted ventilation with periodic hyperinflations of the patient's lungs may prevent the evolution of the lung lesions associated with this condition.

DR. SMITH: I would like to thank Dr. Murray for his superb summary of this complex problem. We have time for one or two questions.

DR. HAVEL:\* Please comment on the possible prevention of pulmonary fibrosis by glucocorticoids.

DR. MURRAY: I believe the pulmonary fibrosis that occurs is a nonspecific consequence of the injury to the lung parenchyma. Fibrosis occurs following infection or infarction and also may be caused or aggravated by oxygen toxicity and other factors. So far as I know, it has been impossible in most clinical situations to prevent the development of fibrosis by steroid administration. The only data with which I am familiar show that the use of steroids accelerates and magnifies the lung injury from oxygen toxicity. I do not think corticosteroids should be given in shock lung in view of our knowledge today.

QUESTION: Please comment on the use of urokinase or thrombolytic agents early in the syndrome.

\*Richard J. Havel, M.D., Associate Director, Cardiovascular Research Institute, and Professor of Medicine.

DR. MURRAY: Again one faces the problem of interrupting the clotting mechanism in persons who may have hemorrhagic problems. There is a large cooperative study in progress on the role of fibrinolysis in pulmonary embolism. Although preliminary results are promising, conclusive information on their value is not yet available. It would be preferable to avoid the administration of pharmacologic agents of that sort.

QUESTION: Would you comment on the role of the sympathetic nervous system in the venular constriction?

DR. MURRAY: The role of venular constriction is very hypothetical. There is debate as to whether pulmonary veins actually have the capacity to constrict. There is considerable species difference in the extent of pulmonary venoconstriction under different pharmacological and physiological stimuli. So far as I know, no one has determined that pulmonary venular constriction in humans causes the vascular congestion and other findings described. At this stage of our knowledge, drug therapy should be based on the patient's underlying condition and not directed toward interrupting the pulmonary vascular responses.

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#### IF THE UPPER LID, ALLERGY; IF THE LOWER, IRRITATION

"If you're treating a patient with corneal or conjunctival infection and he is allergic to the drug, his upper lid will usually be swollen. If his eyes are irritated or he's just having a secondary irritation to the drug, it'll be mostly on the lower lid. This is a little feature that you might remember."

—BYRON H. DEMOREST, M.D., San Francisco  
Extracted from *Audio-Digest Ophthalmology*,  
Vol. 7, No. 2, in the Audio-Digest Foundation's  
subscription series of tape-recorded programs.

# RELEVANCE



## today and tomorrow

## in Medical Education

### A FORUM WITH A PURPOSE

*Students of today question the relevance of much of their formal education. In medical schools the concern is particularly with the relevance of the educational experience to the professional commitment in modern society. To engender discussion of the subject, CALIFORNIA MEDICINE in its January issue printed eight essays by authors known to have keen interest in the subject.*

*Readers in California and elsewhere are invited to take part in a continuation of the forum in succeeding issues. The following are contributions selected from those received to date. Others will be published in the months ahead. At an appropriate time the material will be collated and, if feasible, the distillate will be prepared in the form of a statement.*

*If you have thoughts on the subject, just address them to the editors of CALIFORNIA MEDICINE, 693 Sutter Street, San Francisco, California, 94102. Keep your essays short, please.*

#### DONALD W. PETIT, M.D.

*Alhambra*

*Clinical Professor of Medicine, University of Southern California School of Medicine, Los Angeles; Consultant, Committee on Continuing Medical Education of the Scientific Board, California Medical Association*

THE THOUGHTS expressed in the forum are many and varied. It seems to me that two of the most significant came from John Millis and Paul Sanazaro. Dr. Millis in his statement "The weakness of medical education is not so much irrelevance but rather omission and incompleteness" and the data that he used to back this up seemed to be most appropos.

Dr. Sanazaro's statement that "Relevance, like beauty, is often in the beholder's eye" is expanded upon at some length by W. D. Maxwell in the *Bulletin of the American Association of University Professors*, "Some Dimensions of Relevance," Vol. 55, p. 337-341, September 1969. In this article, Dr. Maxwell had posed to his students the question regarding what constitutes a relevant course and found that there was no simple answer to this question. He came to the rather penetrating conclusion: "There is no objective relevance—that the relevance of a topic, course, curriculum, or the entire educational experience (in their view) can only be judged by the individual in terms of *his* view of society, *his* goals, *his* aspirations, and *his* expectations." It is obvious that if one accepts this—and I feel that one must—then the matter of relevance must be a sort of composite point of view made up from many sources.

In this context, the matter of relevance in continuing education has a great deal to do with what one might call coordination of continuing education. Thus, the relevance of our continuing education exercises are going to depend upon the coordination that is achieved between several types of needs and facilities, and these may be listed briefly as coordination between the purveyors of continuing education as to time and place; coordination of such courses with physicians' needs as perceived by them and as discovered by techniques such as self-assessment examinations and medical audit courses; coordination between courses, physicians' needs and patient needs, the latter to be determined on the basis of interview techniques, morbidity, mortality, statistics, community survey and the like. All of this must, in turn, be coordinated with the environment with which a physician is going to work. It will do little good to determine needs and to coordinate courses if those that are given do not relate to the type and place in which practice will be carried forth.

Finally, continuing education for the physician must be coordinated and, therefore, be made relevant to the educational background that he himself has had in earlier years as well as other workers in the health field with whom he must work and cooperate in order to achieve success.

If continuing education is to be relevant, it must have certain characteristics that will come through regardless of the system, situation, or place in which the physician or other health professional works. The end result of such education should be a strengthening of the motivation for



that person to give of himself one step more than might be required. The motivation to "walk the second mile" or as they say in athletics, to give a "great second effort" is badly needed. Without this, no system will work. With it, almost any system will work. There has been little emphasis placed upon those factors that stimulate the individual physician to care about his individual patient. Most physicians care and care deeply. Is this purely an emotional response? Is this a product of the fee for service system? Is it related to some inherent attitude toward other people? It is a fertile field for behavioral research and it is one that at this time is sadly neglected.

### IAN M. SCHILLER, A.B.

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*Second Year Medical Student, University of California  
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Student Representative, Committee on the Role of Medicine  
in Society, California Medical Association*

MEDICINE IS PERHAPS unique among human endeavors in that its practitioners, by seeking to eradicate disease, are laboring so that their profession ultimately will become obsolete. Mr. Stalcup\* recognizes the improbability of achieving this total obsolescence of physicians even in the ecologically balanced society of the future when he suggests that there still will be a need for "disease specialists, to manage those who are essentially treatment failures of the health specialists." It appears undesirable to alter medical education so drastically that the physician would become a "physician to the environment," and highly unlikely that this goal could be reached. Education of a physician to the environment implies the development of a super-generalist competent as city planner, economist, social worker, public health nurse, social psychologist, etc. Considering the rapid growth of each of these occupations, one finds it difficult to conceive of a health specialist embodying all their skills and knowledge.

The physician of the future must be educated to function as an integral, but not necessarily controlling, member of a broadly based health team comprising not only participants from the traditional medical and paramedical disciplines, but also social scientists, city planners, and representatives of the community. To this end, the physi-

cian must come to medical school with a grounding in the special fields of the non-medical members of the team sufficient to make him conversant with the goals, problems, and methods of these disciplines and to enable his continuing education therein; but his primary training must continue to be concerned with the more traditional sciences and arts of prevention, diagnosis, and treatment of the immediate causes of illness. Not all disease may be attributed to the effects of environment; there will always be some dysfunction and malady requiring the attention of the clinician.

Thus far in this FORUM there has been relatively little discussion of relevance for today in medical education, an omission of particular concern to the somewhat myopic eye of this second year medical student! Relevance is not so much the issue as are the methods and emphases of current medical education. For example, the half-life of facts now taught in medical schools is variously estimated to lie somewhere between five and twelve years. If that is true, then much of what is taught to the medical freshman today will be outmoded and replaced before he has completed his residency. Moreover, only a very limited

number of facts can be introduced effectively during the course of a formal medical education—this amidst an explosion of scientific knowledge and methods with which the conscientious physician must grapple. One solution to this problem is to recognize that the physician is not only a technician, but also a scientist and creative thinker, whose education (rather than training) should center on problem-solving, analysis of concepts, i.e., active participation in a learning process which will continue throughout his career. To this, some readers will immediately rebut, "Yes, but one can't cope with the principles and ideas until he has developed a functional vocabulary." If one recognizes pre-clinical and much of clinical training as the development of a language, then one may accept the idea that in learning a language one first masters its grammar—a framework of concepts and principles. Although this clearly requires the simultaneous acquisition of a limited vocabulary, the most effective way to build a functional vocabulary is to actively use the language by associating words with observed objects and actions. The grammar provides a rational system into which one fits all subsequently learned words.

If efficient use is to be made of our limited educational facilities and teachers, there must be a fundamental change in an educational philosophy based on memorization of multitudinous facts which are to be dredged up miraculously several years later when their application becomes necessary. It may be superfluous to note that this argument does not impugn the relevance of the materials presented in most medical classes.

Our entire educational system—from kindergarten through graduate school—has often been criticized for stifling initiative and creativity and for failing to take advantage of whatever motivation students inherently possess. The latter criticism is particularly applicable to medical education, because a fundamental concept of the psychology of learning is overlooked.

A child begins to learn when something he observes arouses his natural curiosity, and he is motivated to ask questions or to seek answers more directly through experimentation. This process is often destroyed by a rigid educational system which demeans the satisfaction of acquiring knowledge, in favor of external goals such as grades. Similarly, the entering medical student is motivated to ask questions. If exposed to living patients from the start, the student is very likely to want to know what illness the patient has, what its cause is, what the microscopic appearance of the lesion is, what biochemical processes are involved, etc. A natural sequence of questioning leading to answers is begun.

The rigid program of two pre-clinical years preceding two clinical years reverses this order: an attempt is made to provide information ("answers") before the motivating questions have entered the student's mind! Fortunately, many schools are coming to this realization and are introducing both greater flexibility and integration of pre-clinical and clinical sciences into their curricula.

Finally, there remains the question of proper allocation of emphasis on various topics in medical education. Foremost among the problems is the insidious pressure on the medical student to either specialize or to become a researcher. This pressure is in total contradiction of the oft-voiced goal of the medical community to improve delivery of medical care. Research is essential, but not all the best minds should be shunted to this one aspect of medical care. Properly trained family practitioners are essential to the satisfactory development and maintenance of community health.

In the fervent production of a highly skilled corps of super-specialists, the medical school often neglects education in the humanities, particularly philosophy and ethics. The result is untenable: physicians able to routinely perform organ transplants, prolong the lives of physical beings no longer capable of living, disturb the ecological balance and factors of natural selection, but unable to cope with the gigantic social and psychological dilemmas these skills pose. Herein lies the greatest need for an immediate change of emphasis.

\*CALIFORNIA MEDICINE 111:6, 1970.



**ARTHUR H. COLEMAN, M.D., J.D.**

*San Francisco*

*Medical Director, Hunters Point-Bayview  
Community Health Service*

IT WAS INTERESTING to compare the thought processes of the over-thirty-years-of-age physicians with those of the students, presumably under thirty. True to form, the former, although endorsing change, sought it in a more conservative manner. Stalcup's recommendations, on the other hand, bordered on being revolutionary.

To see this bi-polar thinking is the crux of our problem these days; *i.e.*, how can we bridge the gap between the two. I would not urge the immediate discarding of our present form of medical education—it might be bad, but, at least it is orderly. As much as change is needed, to do it overnight would lead to chaos. This, however, is not meant to be an invitation to keep talking about what has to be done and never doing it.

It appears to me that what is relevant is action—action which shows good faith and is meaningful. Thus, a number of institutions (I would like to see the University of California Medical Center in San Francisco as one of them) should immediately divert some of their research funds for disease to a research project which would lead to the opening of a second medical school on the campus to employ some of the newer concepts about the relevant medical education suggested by the authors.

Why not a three-year medical school to train Humanists or Family Physicians and let the four-year school remain, though progressively modified, to train the super-specialist, the theorist, the researcher, the academician. It is recognized that there would be a licensing problem to overcome with such a proposal. Licensing, in its present state, has not been very relevant in helping to meet the manpower needs of many communities, and, allowing for new careers.

People are different. There is no reason to force all students to be only social-issue-oriented any more than it has been wrong in the past to direct students to be, as Stalcup so morbidly puts it, "death specialists."

It would be difficult to offer such flexibility in one institution; thus, the recommendation for two institutions. The new school, as suggested, could be on a small experimental basis.

"Relevance for Today and Tomorrow in Medical Education" must recognize that students, like human beings, which they are, range from one end of the pole to the

other, in all things. Perhaps the mistake, in the past, has been that we have lumped all medical students in the middle; therefore, education has not been relevant for many of them.

**GEORGE C. GRIFFITH, M.D.**

*La Canada*

*Professor of Medicine (Emeritus), University of Southern California  
School of Medicine*

IN MY INTERPRETATION, relevance in medical education means that which pertains to or is applicable to the learning process. Ultimately, this learning process should lead to a complete understanding of life and living.

Medical education must add to the old and current information the techniques for the prevention and cure of disease. Scientific facts alone cannot provide the complete, meaningful education, for to attain that goal the mind of the learner must possess qualities of curiosity, facility, flexibility, imagination, and an insight for creativity. With these germane qualities as a background for a continuing lifetime medical educational process, the learner will be provided with the tools for the development of new information and new techniques for the advancement of human welfare. The spectrum of life must be constantly studied so that basic scientific facts can be applied to the full life pattern.

I believe that the trend of relevance in medical education today is toward producing a physician who is public health minded and is oriented toward the prevention of disease through control of abnormal ecology and environment. Society has created the physician—the healer of the sick. In making medical education more relevant to the needs of society, the physician must work with the public health officials, sociologists, psychologists and economists, but he, the physician, will always remain, in large measure, a healer of the sick.

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# Important Advances in Clinical Medicine

*The Scientific Board of the California Medical Association presents the following inventory of items of progress in clinical medicine. Each item, in the judgment of a panel of knowledgeable physicians, has recently become reasonably firmly established, both as to scientific fact and important clinical significance. The items are presented in simple epitome and an authoritative reference both to the item itself and to the subject as a whole is generally given for those who may be unfamiliar with a particular item. The purpose is to assist the busy practitioner, student, research worker or scholar to stay abreast of these items of progress in clinical medicine which have recently achieved a substantial degree of authoritative acceptance, whether in his own field of special interest or another.*

*The items of progress listed below were selected by the Advisory Panel to the Section on Internal Medicine of the California Medical Association and the summaries were prepared under its direction.*

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## Vasopressin Test for Assessment of Integrity of Pituitary-Adrenal Axis

The vasopressin test offers a new and easier method for the assessment of integrity of the pituitary-adrenal axis. Vasopressin is similar in action to corticotropin-releasing factor which is normally manufactured in the hypothalamus and acts on the pituitary to cause it to produce ACTH. The test is performed by injecting 10 units of aqueous vasopressin (Parke, Davis & Company) intramuscularly. Plasma cortisol is determined immediately before and one hour after the vasopressin injection. If the pituitary is intact the plasma cortisol concentration in the one-hour specimen should be twice that of the baseline specimen.

GRANT GWINUP, M.D.

### REFERENCE

Gwinup G: A test for pituitary function using vasopressin. *Lancet* 2:572-3, 1965

## Diagnostic Application of Immunoglobulin Determinations

The simplicity with which immunoglobulins may now be measured through radial immunodiffusion techniques has led to rapid accumulation of knowledge concerning changes in immunoglobulins in a host of clinical disorders. Absolute values of the specific  $\gamma$ -globulin deficiencies in instances of hypogammaglobulinemia may be readily determined by radial immunodiffusion and replacement therapy appropriately determined. In the hyperglobulinemic disorders (e.g., myeloma and macroglobulinemia), the effectiveness of such therapeutic modalities as chemotherapy and plasmapheresis can be similarly followed. Chronic infections and several other "reactive" disorders (e.g., auto-immune diseases) characteristically show increased  $\gamma$ G levels. Changes in  $\gamma$ A-globulin levels are specifically noted in Laennec's cirrhosis where the levels are

increased, and in hereditary ataxia telangiectasia where the values are diminished or absent. In the nephrotic syndrome,  $\gamma G$  and  $\gamma A$  levels are low but the  $\gamma M$  fraction is normal or slightly elevated. In protein-losing enteropathies, all serum immunoglobulins may be low. Elevation of IgM levels during the neonatal period is indicative of congenital infections. Marked elevation of IgM levels occur in systemic parasitic infestations, the presence of IgM in spinal fluid being considered presumptive evidence of trypanosomiasis in Africa. More recently, elevated IgM levels have been used to differentiate infectious from serum hepatitis.

EDWARD SHANBROM, M.D.

#### REFERENCE

Lou K, Shanbrom E: Immunodiffusion techniques in clinical medicine. II. Radial immunodiffusion. *JAMA* 200:323, 1967

## Value of Total Thyroxin and Free Thyroxin Measurements in Thyroid Evaluation

The protein-bound iodine (PBI) and radioiodine (RAI) uptake can be altered by numerous substances even though no abnormality of the thyroid gland exists. Availability of total serum thyroxin and free serum thyroxin measurements now provide more accurate means for evaluating the thyro-metabolic status. With excessive inorganic or organic iodides, especially iodinated radiographic dyes, the PBI is elevated and the RAI uptake decreased. Measurement of total serum thyroxin eliminates all exogenous sources of iodide and measures only thyroxin iodine. With abnormal binding of thyroxin to serum proteins, the PBI may be increased (oral contraceptives, pregnancy) or decreased (androgens, Dilantin,<sup>®</sup> nephrosis). The free thyroxin level determines the amount of metabolically active hormone (free thyroxin) present even though total thyroxin levels may be altered by abnormal binding to serum proteins.

WINSTON A. TUSTISON, M.D.

#### REFERENCES

Sterling K, Brenner MA: Free thyroxine in human serum: Simplified measurement with the aid of magnesium precipitation. *J Clin Invest* 45:153-163, 1966

Murphy BEP, Pattee CJ, Gold A: Clinical evaluation of a new method for the determination of serum thyroxine. *J Clin Endo* 26:247-256, 1966

## Clinical Indications for the Analysis of Immune Globulins

Quantitation of specific immunoglobulins is helpful in the evaluation of three classes of patients: (1) the patient with a suspected immunoglobulin deficiency syndrome who presents with recurrent infections; (2) the patient with hyperglobulinemia; and (3) the newborn in whom an intrauterine infection is suspected.

1. Immunoglobulin deficiency syndromes may be either congenital or acquired and may demonstrate a selective or combined deficiency of either IgG, IgA, or IgM. Those deficient in IgG may be helped substantially by parenteral gamma globulin.

2. Patients with hyperglobulinemia fall into two classes, those with malignancies of the lymphoreticular system exemplified by multiple myeloma and those with an increase in all immunoglobulins such as in hepatitis and chronic infectious processes.

Patients with myeloma and hyperglobulinemia usually have a selective increase in IgA or IgG with a depression of the other immunoglobulins.

3. The newborn usually begins synthesizing IgM around the time of birth. If exposed in utero to infections such as rubella, cytomegalic inclusion disease, or toxoplasmosis, significant IgM will be synthesized and appreciable levels will be found in cord blood.

J. E. LEWIS, M.D.

#### REFERENCE

Fahey JL: Antibodies and immunoglobulins. II. Normal development and changes in disease. *JAMA* 194:255-258, 1965

## Phosphate Treatment Of Hypercalcemia

Hypercalcemia may occur in a variety of conditions including parathyroid adenoma, carcinomatosis, vitamin D intoxication, and immobilization of patients with Paget's disease. Hypercalcemia causes symptoms such as constipation, lethargy, lassitude, and in more severe conditions, nausea, vomiting and dryness of the mouth. Inorganic phosphate given orally or, in an emergency, intra-



venously has been found to be effective in lowering the serum calcium without producing soft tissue calcification. Orally a phosphate powder preparation (Hyper-Phos®) provides 100 mg of phosphorus per capsule. Initially ten capsules and later up to 30 capsules are given daily to control the level of serum calcium.

PHILIP CORR, M.D.

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 Goldsmith RS, Ingbar SH: Inorganic phosphate treatment of hypercalcemia of diverse etiologies. *New Eng J Med* 274:1-7, 1966

## Disaccharidase Deficiency: A Clinical Reality

Recognition of intestinal disaccharidase deficiency (particularly lactase) as a cause of symptoms in the newborn has long been accepted as a clinical entity. Acceptance as a syndrome in the adult has, at best, been recognized for only a decade. It occurs in 5 to 20 percent of Caucasians and 60 to 90 percent of non-Caucasians. It would appear mandatory that clinicians study those patients with clearly defined symptoms (diarrhea, abdominal distension, flatulence, abdominal colic) of unproven cause for disaccharidase deficiency. Recent studies show that patients with acute enteric diseases of known cause may show persistence of disaccharidase deficiency long after the cause of the primary disease has been eliminated. Disaccharidase deficiency should be considered in patients with (1) psychophysiologic gastrointestinal disease, (2) those with persistence of an "irritable bowel syndrome" after an acute intestinal upset of known cause, and, (3) patients with postoperative "dumping syndrome." Bayless and co-workers have outlined workable criteria for establishment of the diagnosis of lactase deficiency in the adult.

ROBERT J. BOLT, M.D.

#### REFERENCES

- Gray GM, Walter WM Jr, Colver EH: Persistent deficiency of intestinal lactase in apparently cured tropical sprue. *Gastroent* 54:552-558, 1968  
 Bayless TM, Rosensweig NS, Christopher N, et al: Milk intolerance and lactose tolerance tests. *Gastroent* 54:475-477, 1968

## The Clinical Use of Medium Chain Triglycerides

Although medium chain length triglycerides (MCT) have certain characteristics which offer potential therapeutic benefit, the therapeutic utility of MCT has been somewhat less than might have been anticipated from knowledge of physiological behavior. The most encouraging reports have come from the use of MCT in patients with chylous ascites, chyluria, or chylothorax. MCT have also been used in treatment of malabsorption syndromes of various causes with some beneficial effect on severity of diarrhea and steatorrhea. However, isocaloric substitution of MCT for long chain triglycerides has rarely led to weight gain, and the use of MCT in patients with malabsorption should probably be limited to clinical situations in which effective conventional therapy has either failed or does not exist. MCT should probably not be used in patients with active inflammatory bowel disease or hepatic encephalopathy.

GERALD REAVEN, M.D.

#### REFERENCE

- Greenberger NJ, Skillman TG: Medium chain triglycerides. *New Eng J Med* 280:1045-1058, 1969

## Indications for Pacemakers In Cardiac Disease

Artificial pacemakers may be indicated in a number of diseases which result in bradycardia. As a general rule the bradycardia should be accompanied by symptoms, either Adams-Stokes attacks or congestive heart failure. The following are included in this category: second and third degree atrioventricular block, first degree atrioventricular block with bundle branch block, sinoatrial block and sinus arrest. On rare occasions unresponsive tachycardia may be controlled by an artificial pacemaker.

MICHAEL BILITCH, M.D.

#### REFERENCES

- Bilitch M, Lau FYK, Cosby RS: Recent advances in artificial pacemakers. *Calif Med* 107:164-170, 1967  
 Pomerantz B, O'Rourke RA: The Stokes-Adams syndrome. *Amer J Med* 46:941-960, 1969

## Diagnosis and Treatment of Growth Hormone Deficiency

Growth retardation may be secondary to a variety of diseases including growth hormone deficiency. This most commonly results from tumor or an idiopathic pituitary defect and may be associated with deficiencies of ACTH, thyroid-stimulating hormone and gonadotropins. Plasma growth hormone is measured by immunoassay techniques. Fasting growth hormone concentrations are normally very low. Therefore stimuli which are known to elicit growth hormone secretion are utilized to unveil deficiency. Subnormal growth hormone responses to hypoglycemia induced by intravenous insulin and to arginine infusion establish the diagnosis. Administration of human pituitary extracts may establish normal growth over periods of several years.

MICHAEL PERLEY, M.D.

### REFERENCES

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- Kaplan SA: Human Growth Hormone. Disease-A-Month. Chicago, The Yearbook Medical Publishers Inc, Dec 1968

## Treatment of Hemophilia With Newer Blood Factors

The management of the hemophilic patient has taken great strides in recent years. Fresh frozen plasma remains the agent of choice in the control of minor bleeding and hemarthroses. The introduction of partially purified protein fractions derived from human plasma has facilitated considerably the management of the severe bleeder, as well as providing specific therapy directed toward the particular type of hemophilia. Cryoprecipitates and AHG concentrates are commercially available for use in Factor VIII (AHG) deficiency. Elective operation can now be performed in cases which hitherto had a high mortality. These agents also show promise in the management of hemophiliacs with acquired resistance to plasma infusion. Recently a stable purified prothrombin complex has

been introduced which has proven efficacious in the treatment of Factor IX (PTC) deficiency.

GARSON H. TISHKOFF, M.D.

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- Rizza CR, Biggs R: The use of plasma fractions in the treatment of hemophilia and von Willebrand's disease, *In* Brown EB, Moore CV (Eds): Progress in Hematology. New York, Grune & Stratton, 1969
- Hoag MS, Johnson FF, Robinson JA, et al: Treatment of hemophilia B with a new clotting-factor concentrate. *New Eng J Med* 280:581-586, 1969

## Suppression of Rh Sensitization

It is now possible to prevent hemolytic disease of the newborn caused by the principal Rh factor. This prevention is accomplished by the prompt destruction of fetal red cells which normally enter the maternal circulation at delivery and stimulate the mother to produce Rh antibody. This destruction of fetal cells is accomplished by the use of a potent anti-Rh gamma globulin.

WILLIAM M. TODD, M.D.

### REFERENCES

- Jennings ER: Recent advances in diagnosis, treatment, and prevention of hemolytic disease of the newborn, Ch 12, Progress in Clinical Pathology. New York, Grune & Stratton, 1965
- Jennings ER, Dibbern HH, Hodell FH, et al: Prevention of hemolytic disease of the newborn. *Calif Med* 110:130-133, 1969

## Use of Plasma Renin Assays In the Evaluation of Patients With Hypertension

The development of reliable methods for the determination of plasma renin has improved the reliability of diagnosis in two types of curable arterial hypertension. The normal stimulus for renin release is a decreased "effective blood volume." If renin secretion remains high despite plasma expansion with salt and water and the maintenance of bed rest, it is probable that an

obstructive reno-vascular lesion is present which creates the impression of volume depletion at the renin secretion site (the juxta-glomerular apparatus). The diagnosis is further supported if the renin in the renal vein blood from the suspect kidney is at least one and a half times as concentrated as that in the venous blood from the other kidney. On the other hand, the aldosterone-secreting tumor of the adrenal inhibits the release of renin by preventing the normal stimuli. Thus, if renin secretion remains low despite sodium depletion, potassium supplementation and exercise, the diagnosis of an aldosteronoma is supported.

RALPH GOLDMAN, M.D.

#### REFERENCE

Haber E: The renin-angiotensin system in curable hypertension. *Mod Conc Cardio Dis* 38:17-22, 1969

### The Clinical Use of Propranolol

Propranolol reduces rhythmicity and myocardial contractility by blocking the cardiac beta-adrenergic receptor sites. The ventricular rate has been shown to be significantly reduced in atrial tachycardias, flutter, and fibrillation by oral or parenteral administration. Hypertensive patients have demonstrated systolic and diastolic pressure reductions of approximately 10 mm (mercury) with 120 mg per day orally. Coronary artery disease patients have observed increased exercise tolerance and diminished frequency of anginal attacks with from 40 to 160 mg per day.

The side effects of severe bradycardia, gastrointestinal pain, and congestive failure have been noted in some patients at the higher dose levels.

ALLEN BOWYER, M.D.

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Harrison DC, Griffin JR, Fiene TJ: Effect of beta-adrenergic blockade with propranolol in patients with atrial arrhythmias. *New Eng J Med* 273:410-415, 1965

Dwyer EM Jr, Wiener L, Cox JW: Effects of beta-adrenergic blockade (propranolol) on left ventricular hemodynamics and the electrocardiogram during exercise-induced angina pectoris. *Circulation* 38:250-260, 1968

Richardson DW, Freund J, Gear AS, et al: Effect of propranolol on elevated arterial blood pressure. *Circulation* 37:534-542, 1968

### The Pathogenic Role of the EB Virus

Studies reported over the last year have strongly implicated the EB (Epstein-Barr) virus in the pathogenesis of infectious mononucleosis. The agent is not antigenically related to any known herpes virus but has been also isolated from Burkett's and other tumors, although here there is no convincing evidence for its etiologic role. Infectious mononucleosis only occurs in antibody-negative persons and after this disease antibody titers which are elevated for life, can be sensed by complement fixation and indirect fluorescent antibody assay. Antigen associated with the agent has been seen in white blood cells during infectious mononucleosis and typical symptomatology was produced in a single patient by administration of the EB virus.

THOMAS MERIGAN, M.D.

#### REFERENCES

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Niederman JC, McCollum RW, Henle G, et al: Infectious mononucleosis—Clinical manifestations in relation to EB virus antibodies. *JAMA* 203:205-209, 1968

### Amniocentesis

For the woman who has produced anti-Rh antibody a major problem is death of her offspring, either intrauterine or shortly postpartum. A major factor in outcome of the pregnancy is the estimation of the degree of affliction of the fetus. Examination of amniotic fluid has contributed greatly to the solution of this problem.

WILLIAM M. TODD, M.D.

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Jennings ER, Dibbern HH, Hodell, FH, et al: Prevention of hemolytic disease of the newborn. *Calif Med* 110:130-133, 1969



## Effective Drug Therapy For Hyperlipidemia

It is now the consensus that drug therapy of hyperlipidemia should be preceded by specific diagnosis. Primary hyperlipoproteinemia due to one of the five phenotypes should be differentiated from secondary hyperlipidemia due to myxedema, diabetes, etc. Secondary hyperlipidemia is treated by treating the underlying cause. Of the primary Types, I responds to low fat diet; II responds to a polyunsaturated fat diet plus oral bile acid bind-

ing resin therapy; III responds to weight loss and Clofibrate; IV responds to dietary restriction of carbohydrate, and Clofibrate; and V is a mixed classification. No single agent appears suitable for all Type V patients.

DAVID H. BLANKENHORN, M.D.

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Levy RI, Fredrickson DS: Diagnosis and management of hyperlipoproteinemia. *Amer J Cardiol* 22:576-583, 1968

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### Bacteria in Sputum— Contaminants or Culprits?

THE FREQUENCY with which infection must be evaluated as a primary or secondary factor suffices to establish its importance in lower respiratory tract disease. Bacterial infection is also one of the major aspects of pulmonary disease of all sorts for which well designed specific treatment may provide significant benefit—and, contrariwise, harm to the patient may follow from inappropriate antimicrobial therapy. Accurate microbiological diagnosis of the agents present in respiratory tract secretions and appraisal of their significance consequently assume paramount importance. The deficiencies in the methods we employ for this (see Hoeprich's article in this issue) suggest we either do not always recognize the extent of the challenge or we are too lazy or too esthetically sensitive to use the methods necessary to provide a satisfactory answer for the problem. To assess the role of bacterial infection in lower respiratory tract disease and to decide whether and what antimicrobials are indicated, the physician must ask himself whether infection exists at all and if so what microorganisms are responsible for it.

In the majority of primary pneumonias these questions can probably be answered from the clinical and radiologic findings and good stained smears of purulent sputum, the results being confirmed by culture. When indications arise for the use of antibiotics in the course of chronic lung disease, these questions can ordinarily be answered on the basis of statistical data applying to this problem similarly confirmed by x-ray findings and stained smears and cultures of purulent sputum. Hoeprich has pointed out, however, that additional methods may be essential when it is necessary to distinguish organisms which originate from the lower respiratory tract passages from those which may contaminate the sputum from supralaryngeal areas. The distinction is especially important when the patient has responded poorly to antimicrobial therapy and concern exists that superinfection may have arisen in the lower respiratory tract. It is likely that better methods for bacteriologic study of sputum should be employed more rather than less frequently than is currently common practice.

Remarkable cleansing mechanisms preserve sterility of the normal tracheobronchial tree below the larynx. With only a few exceptions, most notably tuberculosis, some acute or chronic injury which alters the normal anatomy and physiology of the respiratory tract is required before bacterial infection occurs. When purulent secretion—that is, sputum—results, the bacteriologist is usually asked to perform a culture and is expected to select portions suggesting purulence. Stained smears may or may not be prepared and examined carefully, depending upon the compulsiveness of the physician and the quality of the laboratory

operation. Hoeprich and others to whom he refers have established one point with great clarity—expectorated sputum, untreated by washing, does not accurately reflect the bacterial habitants of the lower respiratory tract. Washing of purulent sputum, one of the two most readily available methods of bacteriologic evaluation of the lower respiratory tract, has not achieved much popularity. Possibly this is partly due to its unesthetic qualities, but it also requires more than routine technician attention to the details of washing and selection thereafter of suitable purulent portions for culture; and there is, of course, no guarantee that the material originated from the chest rather than from the paranasal sinuses. Nevertheless, according to some investigators it accomplishes some of the same ends as tracheal aspiration, namely, the removal of oral contaminants, and may be especially useful when combined with examination of stained smears to determine the type of bacteria associated with the polymorphonuclear neutrophils of the exudate.<sup>1</sup> It also has the advantage of not requiring the participation of a physician in obtaining the specimen. More data is needed on the definition of methods and their effectiveness for washing sputum and the comparative value of this with tracheal aspiration.

Once the normal anatomy or physiology of the lung has been altered, either saprophytic or pathogenic bacteria may gain a foothold. This is best exemplified in patients with chronic bronchitis or emphysema when cultures of purulent sputum obtained by tracheal aspiration may show only alpha or non-hemolytic streptococci or *Neisseria catarrhalis*. Stained smears may show the same organisms intimately associated with the polymorphonuclear neutrophils of the sputum. Infralaryngeally in the respiratory tract these bacteria should, therefore, not be regarded as “normal flora” but should be considered as probable infectious agents.<sup>2</sup> This is not to say that more invasive bacteria such as *Diplococcus pneumoniae*, *Hemophilus influenzae*, *Staphylococcus aureus* or *Streptococcus pyogenes* may not often be responsible for infection in these patients. Many of the past and future aspects of the bacterial flora of the respiratory tract have been rather comprehensively reviewed by Austrian.<sup>3</sup>

For the situations Hoeprich has listed in which more definitive bacteriological information is desirable, tracheal aspiration seems the most direct method readily available to all physicians for

evaluating lower respiratory tract infection. The most common indication will be for clarifying a muddled laboratory picture related to the usual aerobic pathogenic bacteria. Tracheal aspiration is a necessity for any cultural studies of anaerobic bacteria which abound in the oral cavity. Negligible amounts of sputum may characterize some cases of early staphylococcal pneumonia, fungus infections or infection associated with severe bone marrow depression. Injection of 2 ml of sterile saline solution into the trachea and then withdrawing it may result in the isolation of a treatable pathogen.

Patients with pulmonary disease with or without sputum in whom infection may or may not play a primary role often receive antimicrobial therapy presumably for infection. Some of these patients may respond poorly because they did not have infection to begin with or did not have the infection for which they were treated. Others, because of alteration of their normal microbial flora or because of the seriousness of their underlying disease, may develop invasive, even life-threatening disease generally referred to as “superinfection.” These are often “super” in the most dramatic sense and are commonly due to bacteria resistant to the antimicrobial being used at the time, mainly, *Staphylococcus aureus* and Gram-negative bacilli. Antibiotic-induced superinfections of the respiratory tract have received recent noteworthy consideration elsewhere by Tillotson and Finland.<sup>4</sup> Of 149 patients with primary bacterial pneumonia, 24 had superinfections and 16 died. Early recognition and prompt adequate treatment provide the major solution to this high mortality rate. Hoeprich alludes to the value of tracheal aspiration in obtaining the information necessary to manage these difficult situations. They are difficult because the organisms involved are relatively resistant to the common antimicrobials used for pulmonary infections and require potentially more toxic antibiotics; and also because it may be extremely difficult on the basis of routine expectorated sputum cultures to distinguish between contamination, colonization and actual infection. This further complicates the choice of the most appropriate antimicrobial agent. In an enlightened editorial dealing with this latter problem, Weinstein and Musher emphasized that failure to distinguish between colonization and superinfection may lead to death from unrecognized or inadequately treated infection or to the unneces-



sary therapy of non-existent disease which may be followed by superinfection.<sup>5</sup> Obviously, the best treatment for colonization is to discontinue antimicrobials and permit the patient to reestablish his normal flora. The distinction between colonization and superinfection proposed by Tillotson and Finland is based upon recurrence of fever, after one or more afebrile days, associated with increased lower respiratory tract signs and symptoms and increased purulence of sputum. Sputum cultures from these patients often reveal many colonies of several resistant bacteria with different patterns of antibiotic sensitivity. Since the relative importance or even infralaryngeal presence of these several types of bacteria may be unclear, the patient often receives simultaneous treatment with more than one antimicrobial at least one of which is potentially quite toxic. Additional studies are needed to establish more clearly the extent to which in this particular situation tracheal aspiration may improve upon early diagnosis by stained smear and be of assistance in resolving the often misleading and time-consuming results of culture.

Hoeprich and his associates have generated some of the best data available in this area, and a reading of his article makes quite apparent some of the shortcomings of the time-honored methods of bacteriological evaluation of lower respiratory tract infection upon which we justify the widespread use of expensive and possibly dangerous antimicrobial agents. It is difficult to escape the conviction that we are failing to employ better methods which are at hand, and reasonably simple as well, and that our clinical judgment needs all the sharpening it can get from the laboratory in managing some of these difficult therapeutic problems. More information is still needed, however, to define the place which these methods should be given in current laboratory practice.

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#### REFERENCES

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2. Mulder J: Bacteriology of bronchitis. *Proc Roy Soc Med* 49: 773-6, 1956
3. Austrian R: The bacterial flora of the respiratory tract. Some knowns and unknowns. *Yale J Biol Med* 40:400-13, 1968
4. Tillotson JR, Finland M: Bacterial colonization and clinical supra-infection of the respiratory tract complication antibiotic treatment of pneumonia. *J Inf Dis* 119:597-624, 1969
5. Weinstein L, Musher DM: Antibiotic induced supra-infection. *J Inf Dis* 119:662-5, 1969

## The Preventability Of Birth Defects

A TENET FUNDAMENTAL to all of medicine is that prevention of a disease is generally to be preferred over treatment, and birth defects are no exception. As is well summarized in the comprehensive review by Bernfield elsewhere in this journal, much of the research in the area of birth defects is at present directed toward an elucidation of the mechanisms which produce these defects and of their underlying causes. However, the overriding hope is that ways might ultimately be found to prevent their appearance, and it is therefore proper to ask whether birth defects are actually preventable. In this discussion, a birth defect will be considered as "a structural or metabolic disorder present at birth, whether genetically defined or as a result of environmental influence during embryonic or fetal life."\* This definition is quite broad and, in addition to structural congenital malformations and prenatally determined retardation, deafness and blindness, includes all genetically determined diseases.

The concept of preventability (not to be confused with treatability) is not an absolute one and must be qualified with regard to the point in time at which prevention is to take place and to the means of prevention that may be used. Preventing conception of a child with a hereditary disease or damage to a fetus by some exogenous agent is quite different from preventing birth of a child with a birth defect. Considering only the former, there are several groups of birth defects which are or will be preventable. These include many of the defects which result from maternal infection, from exposure to teratogenic agents, and from genetic causes such as chromosomal aberrations and abnormalities of specific genes. The possible means of prevention varies with the etiologic factors. For birth defects resulting from maternal infection, prevention involves the identification of

\*Apgar V, Stickler G: Birth defects—Their significance as a public health problem. *JAMA* 204:371-374, 1968

birth defect-producing infectious agents and the development of specific means to prevent fetal exposure. The same considerations apply to teratogenic agents to which fetuses are exposed during development. Many hereditary birth defects can be prevented if parents known to be at risk of having defective children follow the relatively simple although not necessarily pleasant expedient of not having children. This approach is applicable to individuals who are known to be carriers of autosomal "dominant" or X-linked mutant genes and to couples who have already had a child with an autosomal "recessive" birth defect. However, in the latter instance this method of birth defect prevention is somewhat after the fact unless means were used, before child bearing, to recognize those families in which both parents were carrying the same deleterious gene or genes. While it is unlikely that all such genes could be screened, it is possible to visualize the development of automated screening tests for several mutant genes which have reasonably high frequencies in the population.

Fortunately, many birth defects which could result from chromosomal abnormalities are prevented by the spontaneous abortion of the affected embryos early in development. Of the chromosomal disorders compatible with viability, several show a pronounced maternal age effect—the older the mother the greater the risk to the fetus. The prototype of this is trisomy 21 (mongolism) in which the overall incidence is approximately 1 in 600 live births, ranging from 1 in 1,500 for mothers less than 30 years of age to 1 in 60 for mothers 45 or older. Regardless of how advancing maternal age influences the occurrence of trisomy 21, the incidence of the disease could be dramatically cut if women were to have their children during the third decade of life rather than spreading out the child-bearing period over the third to the fifth decades.

Despite the conclusion that many of the birth defects in the categories discussed will ultimately be preventable, there are many which probably will not. For both the infectious and teratogenic causes of defects, preventability requires recognition of the insulting agent, and this might not always be possible. The agent might be so common or so occult as to defy identification, and, as Bernfield points out, prospective studies designed to identify such agents have been unfruitful. Furthermore, hereditary birth defects often arise as

new mutations, and many sporadic defects for which no cause can be discovered may have the same etiologic base. To eliminate this group of defects would require suppression of mutation, a goal that may be neither achievable nor desirable in man. However, it is not suggested that agents such as radiation and chemicals which increase the rate of mutation should not be avoided, since there is little to be gained by deliberately creating mutant genes. The preventability of chromosomal abnormalities, both visible and, for the present at least, invisible, is very much in the same situation as the preventability of single gene mutations, and the same considerations apply.

One group of birth defects that has not yet been considered is that composed of the abnormalities which occur with substantial frequencies and have ill-defined hereditary components. Included are many common congenital malformations such as cleft lip and palate and congenitally dislocated hips. Recurrence risks in families of affected persons are relatively low, generally of the order of 2 to 5 percent, but are definitely greater than in the population at large. Many explanations have been advanced to explain these and other conditions with similar patterns of inheritance: the simultaneous participation of mutant genes at several separate genetic loci (polygenic inheritance); the existence of many different forms of a gene at a single genetic locus; the interaction of genetic factors, whether one or several, with internal and external environmental factors; or, despite the familial aggregation, the operation of environmental rather than hereditary factors. No matter which of these mechanisms is operative, it seems quite unlikely that many defects of the types mentioned will be preventable at the time of their genesis. The recurrence risks are not so great nor the defects so severe as to warrant restriction of family size. The genetic factors are likely to be many and relatively common in the population and therefore not readily controlled. And the environmental factors will to a large extent remain undefined.

Without wishing to appear overly pessimistic, it must be concluded that many birth defects are now and will remain unpreventable if prevention is to occur at or before the time of causation. If prenatal intervention is considered an acceptable mode of birth defect prevention, some but not all of these defects would become preventable. By testing all pregnancies, all chromosomal disorders

could be eliminated. With the development of suitable analytical methods, many hereditary disorders could also be prevented without the necessity for the total avoidance of child bearing. It is quite likely that both chromosomal and metabolic screening could be automated, and technical resources need not be a limiting factor. It is even possible to visualize the development of a fiberoptics amnioscope suitable for use in early pregnancy so that external structural abnormalities not associated with chromosomal or metabolic disorders could be detected. I have deliberately omitted "genetic engineering"—genetic intervention by molecular methods—since its hypothetical role in birth defect prevention, as opposed to treatment, is still very much in question.

The more widely we speculate on what is theoretically possible, the greater the attention that must be paid to questions of ends and means. While no one seriously disputes the desirability of eliminating birth defects, there are some who cannot countenance prenatal diagnosis, with the possible consequence of interference with pregnancy, as a means of doing so. And many of those who do advocate its use would hesitate to apply it to all pregnant women. Even at present, with only a few indications for its use, they are constantly faced by the dilemma of defining a cut-off point, of deciding which conditions are serious enough to merit prenatal intervention and which are not. How much greater will be the problem when many more defects can be discovered early in gestation.

Leaving prenatal diagnosis aside, the same dilemma is inherent in all activities designed to reduce the incidence of birth defects. In which hereditary conditions should families be encouraged not to have children? When should time-consuming and expensive efforts be made to discover environmental factors which might in the end turn out to be uncontrollable? What means of birth defect prevention are truly acceptable? And, considering the likelihood that many birth defects are not preventable, for which defects should efforts at prevention be made at all? These questions are not easy to answer, and many answers that could be given now might change as more information is accumulated. Nevertheless, answers must be found if the all too limited resources of society are to be most effectively utilized

to reduce the incidence of those serious birth defects that are truly preventable.

CHARLES J. EPSTEIN, M.D.  
*University of California  
San Francisco Medical Center*

## Important Advances In Clinical Medicine

THE ADVISORY PANELS to the Scientific Sections which were established during the past year provide a unique resource to the Scientific Board and to the California Medical Association. Each advisory panel is composed of the officers of the section, a representative from the appropriate department of each of California's eight medical schools and a representative from the pertinent professional societies in each specialty as they have been recognized by the Council. Thus each advisory panel reflects the knowledge and experience to be found in academia and in practice—and the base is quite broad.

Elsewhere in this journal (see pages 54 to 59) we are beginning a new feature, "Important Advances in Clinical Medicine," which is made possible only because of the existence and cooperation of these Advisory Panels to the Scientific Sections. Each panel has been asked to identify those recent advances in its specialty which in the judgment of the panelists are truly important in clinical medicine, to epitomize them for the readers of this journal, and in addition to provide references so the reader may readily dig deeper into the specific subject or the general area if it is one with which he is not familiar.

It is hoped that these epitomized items of medical progress, selected as they are by the judgment of very knowledgeable panels in each field of interest, will be helpful to student, teacher and practitioner alike. They should make it easier for him to become aware of what it is he may not, yet probably should know, and to locate the information he will need to catch up with progress in that particular subject. It should make possible more precise use of the time a busy person can devote to "keeping up."



## A Fifth Progress Report

THE COMMITTEE on the Role of Medicine in Society was the first of its kind to be established in any medical association, so far as is known. Since then, there have been others. Through the years the composition of the committee has frequently changed, but it has always had among its members some of the most knowledgeable, experienced and thoughtful persons in the California Medical Association. The assignment has been broad indeed, to examine the constant yet changing role of medicine in a changing yet often confused society, and to suggest ways in which the CMA, its component societies and its member physicians might better play their parts.

There have been several progress reports, each addressed to one or more of the many aspects of the complicated relationship of medicine with today's society. These reports have spanned a time of profound change in the capability of medical science and in public attitudes toward the medical profession and health care in general. The reports have tried to identify what was happening, seek out the causes and to suggest how medicine might deal with at least some of the foreseeable consequences in a positive and productive way.

The *Fifth Progress Report* of the Committee on the Role of Medicine in Society will be published in this journal with the approval of the Council. The first of three parts appears in this issue. The report as a whole examines what the Committee believes must be done if the mainstream of medicine is to serve all Californians in terms of medi-

cine's capabilities in relation to the expectations and demands of today's society. The recommendations of the report have received the endorsement of the Council of the CMA. Their implementation could make a carefully considered concept become a reality, to the immense benefit of medicine and society in California.

## The 99th Annual Session

THE PROGRAM for the 99th Annual Session, to be held in San Francisco March 7 to 11, 1970, is by no means a traditional one. Rather it reflects something of the growing and expanding interests and responsibilities of medicine in today's world. The basic scientific substance of the program remains of a high order, and this is as it should be. But a new flavor has been added. There is considerably more emphasis on various aspects of community medicine and problems in the delivery of health care services. There is even some facing up to the enormity of the population problem and its inescapable effects upon health.

A record number of professional specialty societies and public and voluntary health agencies are participating in some way and for the first time students are listed among the full participants. All of this bodes well for an exciting and productive session. The membership should not only congratulate John B. Dillon and the Committee on Scientific Assemblies of the Scientific Board for setting a new standard for the Scientific Program, but should turn out and reap the benefits as well.

## NEW PAGINATION SYSTEM

To solve a technical problem entailed in an agreement by CALIFORNIA MEDICINE to supply a part of its text section as a supplement to be included in *Arizona Medicine*, beginning with this issue we are changing our system of numbering pages. Instead of the cumulative numbering system used heretofore, wherein each issue (after the first) in a six-month volume began with the page number following the last page of the preceding issue, each month now will begin with page 1. Hence, in citing references to articles that appear in CALIFORNIA MEDICINE beginning with January of this year, the month must be stated in addition to the page numbers. For example, an article in this issue: Bernfield MR: Progress in birth defects research (*Medical Progress*). *Calif Med* 112:26-42, Feb 1970

The National Library of Medicine, which was consulted, has said that the system will offer no difficulty as to indexing in the Cumulative Index.

## Medicine in Society

# The Concept of Mainstream Medicine For All Californians

## Fifth Progress Report of Committee On Role of Medicine in Society

### PART I

*This Fifth Progress Report is to be printed in three parts in CALIFORNIA MEDICINE. Following the appearance of Part III the report will be bound in a pamphlet which may be ordered at \$1 a copy from 693 Sutter Publications, Inc., 693 Sutter Street, San Francisco, California 94102.*

*"A profession has for its prime object  
the service it can render to humanity"\**

THIS REPORT is presented as a logical sequel to the earlier progress reports of the Committee on the Role of Medicine in Society. Its thesis is that if "the American people are committed to a policy of one-class, one-door, high quality medical care available to all, to the limits of our resources, without discrimination on the basis of race, creed, color or economic circumstances," as Anne Somers has stated,<sup>†</sup> then by definition and de facto

this can only be "mainstream medicine." This *Fifth Progress Report* therefore assumes that "mainstream medicine" as we know it today can and must undergo whatever changes are necessary for it to become the instrument through which the national purpose in health care will be achieved. This report will seek to analyze the present situation and to develop in broad outline some of the actions and programs which probably will be necessary in order to reach the goal of "Mainstream Medicine for All Californians."

The previous reports of the Committee provide much of the background upon which this study and its recommendations are based.

• **The First Progress Report** (March 1964) established goals for the Committee and recommended "that the policy of the California Medical Association and of the medical profession of the nation be that of assuring every individual of good medical care by doctors of medicine,

Committee on Role of Medicine in Society: Burt L. Davis, John B. Dillon, Sanford Feldman, Elmer F. Goel, John T. Saldy, Marvin J. Shapiro, Malcolm C. Todd and Malcolm S. M. Watts, chairman; and, ex-officio, Henry V. Eastman and E. Kash Rose.

September 1969

\**Percival's Medical Ethics*, edited by C. D. Leake, Williams and Wilkins, Baltimore, 1927, p. 25.

†Anne Somers, *J. Med. Ed.*, 43:479, April 1968.

and the availability of such professional care when he or she needs it."

¶ **The Second Progress Report** (January 1965) called upon the medical profession to identify with the total medical care problems of society, present creative and constructive programs, strive for a greater consensus within itself, try to revitalize the meaning of the physician-patient relationship and inculcate social roles and responsibilities into the educational process.

¶ **The Third Progress Report** (April 1967) examined the emergence of the concept of health care as a human right and identified certain principles with respect to this which appeared to have general acceptance; recognized the central importance of quality in health care; developed a description of high quality health care, and proposed that a "Quality Assessment Index for Health Care" based on this description be developed; analyzed the strengths and weakness of a "partnership" of medicine with government in a pluralistic society and proposed that medicine's position be strengthened in four specific areas; probed the contemporary scene with respect to organizing for health care, and suggested that perhaps the time had come to encourage the establishment of a "National Academy of Medicine."

¶ **The Fourth Progress Report** (April 1968) noted the infinite scope of the national commitment to health care and finite resources available for this purpose; identified certain value systems which will be applied in decisions concerning allocation of resources; proposed a role of flexible and informed advocacy for organized medicine to bring its knowledge and expertise more effectively to bear in today's pluralistic society and called for an appropriate definition of health, a more precise delineation of the national purpose, and of the scope and responsibility of medicine with respect to this purpose.

Since the last progress report of the Committee a national forum on "The Scope and Responsibility of Medicine" was conducted in CALIFORNIA MEDICINE and a statement on the subject, prepared from published and unpublished contributions, appeared in the December 1968 issue of that journal.

## Comprehensive Health Care

It is clear that "comprehensive health care" also needs definition, but it is not yet clear precisely what this term means. Both the concept and the definition are still evolving. But one can already sense that comprehensive health care is to be equally accessible to all; to be health, rather than disease, oriented; of high quality, and that it will provide a continuum of services rather than episodic care. At its heart there should be a significant relationship between doctor and patient and ready access to the whole spectrum of health care services for every patient. One suspects that comprehensive health care will include not only personal health care, but community, environmental and species health care much as these defined in "The Scope and Responsibility of Medicine" (CALIFORNIA MEDICINE, 109:509-514, 1968).

Whatever its ultimate scope and however it may

eventually be defined, it is "comprehensive health care" which "mainstream medicine" must gear itself to render to all Californians. The overall dimensions of this challenge are certainly obvious enough even though a generally accepted definition may not yet be available.

## The Mainstream Concept

As nearly as the Committee can determine the use of the term "mainstream" to apply to medical care originated within the California Medical Association. A CMA statement issued in 1965 indicates that the term was already in wide usage. The following are quotations from this statement:

"When physicians link the word 'mainstream' with medical care, the implication is that all persons, regardless of age, race or economic status *should* have the assurance of having available to them the same necessary health and medical care resources which are available to the public generally. It is not to be better or less, it is to be the same. Embodied in this concept of 'mainstream' is the idea that care should be available on a continuous and comprehensive basis, not fragmented or sporadic."

"Optimum availability, accessibility and acceptability, maximum economy and maximum quality standards, as well as optimum adaptability to various social, economic and geographic circumstances are best achieved in the 'mainstream' concept, with access to all available forms of services, regardless of source of payment."

"'Mainstream' medical care implies the maintenance of one's dignity while sick, as contrasted with the 'poor house' approach to health care. 'Mainstream' medical care means help near one's home so that a patient need not travel, for example, 100 miles to a county hospital for treatment of a broken hip. 'Mainstream' medical care envisions health facilities and services better planned for and used by all of the people of the community on the basis of their needs and requirements, rather than on the basis of income or resources."

This is the "mainstream" concept. It is voluntary and cooperative in emphasis. It relies more on motivation than compulsion. It is responsive to individual and local needs and situations. Mainstream medicine is dedicated to ensuring equal access, a single level of high quality health services and portability of protection in health care. To accomplish all this will require not only substantial effort at the local level, but also some kind of broad framework of voluntary guidelines within which solutions can be found to local and special problems and responses made to technologic and social change.

The remainder of this report addresses itself to how mainstream medicine as we know it today can be fashioned into an instrument to deliver this "comprehensive health care" to every one who



needs it and thus make "mainstream medicine for all Californians" a reality.

## Some Facts for Today and Tomorrow

The Committee believes that there are a number of facts which must be taken into account which are certain to influence health care delivery to a substantial degree for the foreseeable future:

1. A disparity between the demand and expectations for health care and the resources available for its delivery exists and may be considered permanent for practical purposes.

2. The shortage of physicians will continue indefinitely and may also be considered permanent for practical purposes.

3. There will never be enough specialists in general or family practice produced to act as primary physicians for more than a minority of citizens.

4. The incentives are and will continue to be insufficient to attract physicians in the numbers needed for isolated or deprived communities.

5. Universal coverage for all persons for health care, through either the private or public sector or some combination thereof, is an inescapable corollary to the right of access of all to high quality health care.

6. Financing for health care, from whatever source or sources, will always tend to fall short of increasing demands which result from population growth and technological progress.

7. Value judgments of one sort or another will determine the allocation of relatively scarce resources and services, and moral, humanitarian, social, economic and political pressures may be anticipated at all levels of health care.

The Committee believes that these are among the basic conditions to which mainstream medicine must adjust and within which it must develop itself to provide comprehensive health care for all Californians. The Committee also believes that the present climate is such that no rigid single system of health care can be imposed by government or anyone else, although efforts to do just this are now being made and will surely continue. The play is in the hands of the private sector and the next moves are up to it. It now becomes necessary to try to identify some of the barriers which must be overcome, the tools which are available to mainstream medicine, and the means by which the tools may be applied to overcome the barriers and provide better solutions.

## The Barriers

There is much in the literature about the barriers to equal access of all to health care services and there are many suggestions for overcoming them. (A bibliography will be supplied at end of Part III of this study.) It is unfortunate but true that in general more problems have been exposed than have so far been solved. The Commit-

tee suggests that most of these barriers can be lumped in several categories as follows:

### 1. *The Definition of the Scope of the Problem*

It has not been possible, and indeed it may well never be possible, to define precisely what should be the content or subject matter of comprehensive health care, or to quantitate the true demand for this care or to estimate the resources which are or will be needed to render it. These will always be undergoing change because of technologic progress and changes in the numbers, needs and expectations of consumers.

### 2. *The Interface where Consumer Meets the System*

Many barriers exist at the point where health care is, or should be, sought and received. The evidence is accumulating that personal interest in the consumer and consumer participation are both necessary at these points of contact. The essence of understanding and personal trust inherent in the traditional doctor-patient relationship must somehow be brought to bear at the interface where the consumer meets the system, even though this may be done through aides or intermediaries.

### 3. *The Marketing of Mainstream Medicine*

Mainstream medicine today is not the "non-system" claimed by some of its detractors, but rather its system has failed to reach and win acceptance from major segments of the population. The structure of mainstream medicine needs some alteration for better distribution, as well as better packaging and more aggressive marketing if it is to overcome these barriers and improve consumer acceptance and utilization.

### 4. *Insufficient Resources*

The quantitative insufficiency of resources in manpower, facilities and equipment are and will remain barriers to reaching the national goal, and the situation is not improved when citizens and their government are slow to provide the wherewithal to increase these resources as they are needed.

### 5. *Shortages of Dollars*

It is unreasonable to expect that all the dollars needed can ever be assigned to health care and their comparative lack will therefore always be a barrier to the quality as well as to the quantity and availability of services. It will be necessary to combat this by improving methods of identifying what quality and quantity of services are needed, exposing and correcting waste and inefficiency in governmental and non-governmental programs and negotiating for sufficient funding from public and private sources.

### 6. *Organizational Inertia*

Organizations and institutions of various kinds often develop considerable inherent inertia and are at a disadvantage when the environment with which they must react changes more rapidly than they are capable of adapting to meet the changes. This may occur in business, professional, educational and governmental organizations. It has been happening in both public and private sectors with respect to health care and the barriers which result from this are considerable.

## The Tools

The Committee believes that mainstream medicine already has the essential tools which will be needed but that these tools will require much wider and more imaginative use than has been the case to date if the goal of "mainstream medicine for all Californians" is to be even approximately reached. Like the barriers, the Committee sug-

gests that the tools can be lumped into a number of broad categories as follows:

#### 1. *Data Base*

Accurate facts are among the most essential tools. The Bureau of Research and Planning has pioneered accurate data gathering for the CMA. The value of this tool has been demonstrated many times. Data retrieval is expected to contribute substantially to the data base of mainstream medicine. These should be developed and other instruments should be created as necessary to provide mainstream medicine with an accurate data base.

#### 2. *Information Transfer*

Information transfer or communications is an important set of tools which includes not only professional education and continuing education, health education and public information, public relations, and internal communications, but also an increasing involvement on a participation basis with consumers, community organizations, all aspects of the health care industry, and government. This information transfer is a two-way street and should be considered sensory as well as motor in character. There is need for greater coordination of information transfer in some sort of nerve center.

#### 3. *Aids and Assistants*

The already wide use of mechanical aids and professional and technical assistants in patient care and throughout the health care industry can be extended further as productivity, economy and efficiency require. The principle of delegation of responsibility and authority by physicians to their various assistants is well established in mainstream medicine and its extension should be encouraged rather than viewed with alarm.

#### 4. *Experiment and Innovation*

Experiment and innovation have characterized mainstream medicine. This has been demonstrated in the development of various methods of financing and of new kinds of delivery systems for health care services in California and elsewhere. When soundly based on facts and an accurate assessment of the problem to be solved, experiment and innovation are the approaches most likely to produce successful solutions. Mainstream medicine should build upon its experience and encourage new approaches to the new problems which must be solved in order to achieve the national goals in health care in our pluralistic society.

#### 5. *Advocacy and Accountability*

Since it may be anticipated that health care will usually, if not always, be comparatively underfinanced, with resources in manpower facilities and equipment less than

what is needed to fulfill the public demands and expectations, mainstream medicine will usually, if not always, tend to be on the defensive unless it assumes a public role of advocating what is necessary and accounting to the public for what it has and has not been able to accomplish with the resources actually available. Mainstream medicine must have public understanding and support for its efforts if it is to achieve this goal, and its advocacy and accountability must be clear and in the public interest.

#### 6. *Guidelines and Peer Review*

Experience with guidelines and peer review has proven their value in establishing a level of quality or efficiency without setting inflexible minimum standards which so often turn out to be the maximum level as well as the minimum standard. The CMA has had considerable experience with the use of both guidelines and peer review and these are tools which can be further developed to provide an overall framework for one level of high quality health care throughout California, while at the same time allowing for the local option, local control and local solutions for local problems which are essential to mainstream medicine. (See Part II.)

### Summary of Part I

In this section of the report the Committee sought to (1) establish that "mainstream medicine" is in fact the only instrument which for practical purposes can be developed to render "comprehensive health care" for all Californians; (2) describe something of the climate or situational environment in which this will have to be accomplished; (3) assess briefly some of the obstacles to be combatted; and (4) identify some of the tools at the disposal of "mainstream medicine" which can be further developed to make this health care more nearly a reality for all Californians.

The subsequent section (Part II) will address itself to certain tasks of critical and immediate importance which appear to require concentrated study and prompt development. Part III will propose a comprehensive program for organized medicine in California.

(Part II will be published in the next issue.)

## Professional Corporations

### Tax Questions Still Raised

HOWARD HASSARD, Esq., Legal Counsel, California Medical Association

THE JANUARY issue of CALIFORNIA MEDICINE included an article characterized as "another chapter in a continuing saga" of professional corporations. At the time that article was prepared, the 1969 tax revision bill had just left the Senate Finance Committee, on its way to the joint House-Senate Conference Committee. Last month's article pointed out that the Senate Finance Committee had inserted a provision in the tax bill which would have limited *all* professional corporations to Keogh-type retirement plans. If that amendment had been adopted, shareholders in professional corporations would have been limited to maximum retirement plan contributions on their behalf of 10 percent of compensation or \$2,500, whichever is less. Conventional corporations are able to make tax-exempt contributions of approximately 25 percent of employee compensation. The prospect that the Senate Finance Committee amendment might be included in the final version of the tax revision bill necessitated a warning to all those considering incorporation, since denial of true corporate tax-sheltered retirement programs would deny professional persons what otherwise might be a major incentive for incorporation.

The 1969 tax revision act is now law. When the bill was finally amended and adopted, the Finance Committee's provision was deleted. The Keogh-type limitation which would have been imposed on all professional corporations was not included in the law.

Even though some professional corporations will be able to enjoy true corporate retirement plans (at least for the moment), the new law does contain one important change. Keogh-type treatment has been imposed on Subchapter "S" corporations. A Subchapter "S" corporation is one which makes a statutory election to be treated as a partnership for tax purposes. Corporate net income is taxed as if earned by the shareholders. The tax on earnings which would otherwise be paid by the corporation is therefore avoided. A Subchapter "S" corporation is limited to ten shareholders. Until now, Subchapter "S" corporations have been able to adopt qualified retirement plans, enjoying the right to make tax-exempt contributions of approximately 25 percent of compensation. This is no longer possible. The maximum contribution for Subchapter "S" shareholder-employees is now the lesser of 10 percent of compensation or \$2,500. A professional corporation which wants to enjoy a true corporate retirement plan, with the larger maximum contribution, must also pay a tax on corporate earnings. The same earnings will be taxed again when distributed to the shareholders. If this income is not distributed to the shareholders, there is a risk that the IRS will characterize the corporation as a "personal holding company." The first element in the definition of a "personal holding company" is ownership of more than one-half of the stock vested in five or less persons. This test is met by any corporation with ten shareholders or less. The second element in the definition is that

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the corporation receive its income for personal services under circumstances where the person receiving the services has the right to designate who shall provide them. If this element is also present, a penalty tax of 70 percent on retained income may apply. It has not yet been decided whether a medical corporation might be a "personal holding company," in circumstances where patients regularly select the physicians who treat them.

The purpose of this digression into the "personal holding company" problem is to emphasize the need for competent and continuous tax counsel in this area. This is particularly true when the attitude of the Treasury Department is considered. The Treasury has announced that it will seek additional legislation restricting tax benefits available to professional corporations at the next session of Congress. Both an initial decision to incorporate and the operation of a professional corporation require sophisticated tax advice.

A December decision by the U. S. Tax Court demonstrates both the Treasury's attitude towards professional corporations and the problems physi-

cans can encounter when requisites of tax and corporate law are ignored. A professional corporation established by four radiologists was ignored by the IRS, on the grounds that the physician-shareholders did not in fact conduct their affairs in corporate style. The Tax Court, upholding the IRS, found that each of the physicians, who had separate practices in their own names prior to incorporation, continued to practice in the same manner after incorporation, so that they did not "put flesh on the bones of the corporate skeleton." The corporation was held to be "a mere set of bookkeeping entries and bank accounts."

Some physicians, particularly those in larger groups, will find that incorporation is advantageous for non-tax reasons, such as centralized management. Some physicians, after thorough analysis of their own situation, will find tax advantages in incorporation. Any physician who does decide to incorporate must balance advantages against disadvantages and potential pitfalls, with professional advice initially and continually thereafter, unless there are radical changes in the tax system.

## Attention, Psychiatrists

*Charles W. Socarides, M.D., Associate Clinical Professor of Psychiatry at Albert Einstein College of Medicine, New York City, will speak at the Psychiatry and Neurology Section meeting of the Annual Scientific Assembly, March 9. Plan to attend.*

## Medicine and Human Values

WILLIAM F. JESSEE, *La Jolla*

I WELCOME the opportunity to express the gratitude of the medical student body for the facility which we are dedicating today. We are pleased to receive from the people of California and the United States this first unit of a physical plant which, when completed, will rank as one of the finest in the nation. I cannot but note in passing, however, that this building is but the first of what must rapidly become a four unit medical center. If this institution is to continue to travel up the path of excellence along which it has begun, it must continue to enjoy the unwavering support, both moral and monetary, of the people whom it serves. In order to assure the right of all the people of this community to have access to the finest in health care, it is a necessity that this medical center continue its development as scheduled. Through the construction of this initial facility in the complex, the public has provided itself with a building designed for efficiency, utility and innovation in medical education.

As we formally dedicate this Basic Science Building, I would ask that we give pause to consider the second vitally important component of a university medical center — that is, the people whom it serves: its students, the faculty, and the community-at-large. Without such people, even the finest of facilities is but an empty shell, devoid of value or meaning. The wants and needs, the hopes and fears, the sickness and health of people — that is what the practice of medicine is all about. Medicine is a profession which must strive to be the ultimate synthesis of the highest in humanitarian goals with the finest in scientific knowledge.

We, as students, from our perspective as novices in the order of medicine, perceive the profession as perhaps no other group can. We have been consumers of medical care for more than twenty years. Now we are becoming increasingly involved in the delivery of health services as student physicians. This gives us a truly unique perspective from which we can well understand the needs and desires of both the consumers and the purveyors of medical care. In viewing the health scene of our nation we find, to our dismay, that in recent years scientism as a goal has frequently led to the neglect of the humanism inherent in medical practice; that the *science* of medicine has assumed precedence over the *art* of medicine. We perceive that medical practice should be a balanced alloy of science and art — that neglect of either aspect of the alloy contradicts our definition of medicine and betrays the trust with which we are charged by our patients. In short, we perceive that physicians can no longer concern themselves with the narrowest definitions of medical practice and of the nature of those things which contribute to medical knowledge. The social imperatives of the approaching decade require that we reach out and become ever more involved in the world around us.

It may strike many as unusual that, in dedicating a structure designed for and devoted to the basic medical sciences, I should so heavily emphasize humanism and the medical arts. Indeed, I would be the last to deprecate the value of the basic sciences in the practice of medicine. The alloy must be a balanced one, an amalgam of the finest in medical science with the highest ideals of medical art. Medical art without medical science is, at best, incompetence. And medical science in the absence of medical art is but a mechanical shadow of the true profession of medicine.

The text of an address delivered 26 November 1969, on the dedication of the Basic Science Building, School of Medicine, University of California, San Diego, La Jolla.

The author is a second-year medical student and a member of the charter class at the University of California, San Diego, School of Medicine and is a Life Insurance Medical Research Fellow.

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It is for this reason that we, as students, elected to attend the University of California, San Diego. We believed that this institution, above all others, offered us the opportunity we sought for an education which would be of excellence in every aspect of medical science and medical art. On the whole, we have found that which we sought. We were most fortunate to find a faculty which embodies the finest principles of medicine as I have enumerated them — the highest competence in science with strong feelings of human concern. But this is an age which calls for more than concern — it calls for involvement and *action* in the alleviation of the social ills which plague the health of our nation. Ours is a society which has proved grossly unable to translate its scientific and technological expertise into adequate health care for its citizens. Our record is not a proud one — our country ranks a disheartening seventeenth among the nations of the world in infant mortality, far behind England, Sweden, and other so-called socialist countries. Ours is a nation in which maternal mortality among non-whites is some four times that in the white population.<sup>1</sup> In view of such startling statistics, we have no choice but to ask, "Where has American medicine failed?"

It is the feeling of the medical students of my generation that a primary error has been in the failure of the profession to consider man as a biological whole, molded by his physical and social environments. The complexity of the human body pales in comparison with the intricacies of man's behavior and his modes of social interaction. Through this failure to consider the immense manifestations of man's complex situation, a generation of physicians who are to a large extent ignorant of economic, sociological and ecological aspects of medicine has been produced. Medicine must treat the whole patient; it must become actively involved in selfless efforts to rectify the inequities of the human situation. That the pro-

fession has the capacity for effective social action must not be doubted. In the words of former U.S. Surgeon General William H. Stewart:

"Medicine has a great deal of policy-setting to do, and do quickly, at today's points of interlock between health goals and social goals. We need to develop creative and successful approaches to the delivery of care in the urban slums. We need to deal with the problems of rural medicine. . . . We need to consider the changing relation between practitioners and hospitals. . . . We need to face squarely the problems as well as the advantages of specialization and to strengthen our response to these problems. . . . No professional group that I know has a finer potential for contributing broadly to the formulation of social policy. Academic medicine has everything it needs—except, perhaps, the will and the willingness to enter a new, broader arena—to become a community of social innovators."<sup>2</sup>

I, and the medical students of my generation, would carry the responsibility of the profession one step further. We believe that medicine must concern itself with poverty. Medicine must concern itself with racism. Medicine must concern itself with environmental pollution. Medicine must involve itself with the world as a potent force in effecting social change. We hope that the physicians of our generation shall be the vanguard of a new breed. We hope that we may create a new and higher definition of the word *physician*. We will work, with the guidance and help of our teachers, to insure that all the people of the nation and the world have access to health care of the highest order. A utopian state of health is our goal and no man can find fault in that. If we do not aim for the best of all possible worlds, we cannot hope to shape even a tolerable world.

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# CMA's Certificate in Continuing Medical Education

RONALD L. KAYE, M.D., *Palo Alto*

THE CALIFORNIA MEDICAL ASSOCIATION is formulating a program which will reinforce its commitment to high quality patient care through the physician's continuing medical education. The program will provide formal certification which will serve to acknowledge the accomplishments of California physicians who keep pace with advancing medical knowledge.

The proposed program will serve as a major step in implementation of Resolution 120-69, which was passed by the CMA House of Delegates in March, 1969. Full text of the Resolution is as follows:

### *Resolution 120-69—Continuing Medical Education*

"WHEREAS, the California Medical Association and its component county medical societies have the responsibility to demonstrate to the citizens of California that California physicians possess the most modern medical knowledge; and

"WHEREAS, the California Medical Association and its component county medical societies have a primary responsibility to the citizens of California to assure that the medical care rendered to them is of the highest quality; and

"WHEREAS, the Second Planning and Goals Conference in Continuing Medical Education reaffirmed the long-established policy of the California Medical Association that continuing medical education is wholly desirable and becoming even more necessary to enable the physician to render the best possible medical care for his patients in this day of rapidly expanding knowledge; and

"WHEREAS, the Second Planning and Goals Conference in Continuing Medical Education has recommended that the California Medical Association make available to all physicians practicing in California the

administrative mechanisms to collect, codify and certify participation in accredited postgraduate instruction; now, therefore, be it

"RESOLVED: That this House of Delegates reaffirm the long-established policy of the California Medical Association that continuing medical education is wholly desirable and is becoming even more necessary to enable the physician to render the best possible medical care for his patients in this day of rapidly expanding medical knowledge; and be it further

"RESOLVED: That this House of Delegates direct the Council to develop, with the assistance of the Scientific Board, the specific administrative mechanisms to enable the California Medical Association to collect, codify, and certify participation in accredited postgraduate instruction; and be it further

"RESOLVED: That this House of Delegates instruct the Council to prepare these specific administrative mechanisms for presentation to the 1970 House of Delegates.

"RESOLVED: That the California Medical Association maintain a working relationship with the Board of Medical Examiners on all matters of continuing medical education."

It is in response to this Resolution that CMA is preparing to introduce its formal Certificate in Continuing Medical Education. The new program is now in the final phases of development and will be submitted for final approval to the House of Delegates in March, 1970.

In addition, the new program will reflect the medical profession's own response to increasing consumer concern with the quality of medical care. It will lodge within the medical profession, rather than in governmental agencies, the task of assessing the adequacy of the continuing medical education of California physicians. It is anticipated that such a program will offer a reasonable alternative to the pressure of current legislative proposals which are now pending concerning periodic relicensing of physicians.

The author is the Chairman of the CMA Committee on Continuing Medical Education, and Director of Medical Education, Palo Alto Medical Clinic.

Submitted 18 December 1969.

Reprint requests to: Committee on Continuing Medical Education, California Medical Association, 693 Sutter Street, San Francisco, Ca. 94102.

The proposed new Certification Program has as its goal neither arbitrary regulation nor restriction, but rather the responsible recognition and rewarding of those who maintain high standards in pursuit of self-education. The plan is being coordinated closely with a comparable one by the American Medical Association which recently initiated a Physician's Recognition Award in Continuing Medical Education. It is anticipated that reciprocity will be established between AMA and CMA with respect to these programs to avoid duplication.

The CMA Certification Program, as it will be initially implemented, will represent a flexible and open-minded approach, subject to constant modification. It will encompass continuing medical education of all types, both informal and formal, in which a California physician participates. These are expected to include meetings, programs, and courses sponsored by medical schools, medical institutions, and specialty societies; formally constituted grand rounds; teaching, publication, and research activities; journal clubs and individual reading of journals; audio visual programs, exhibits, and all other known teaching-learning experiences. As new modes of continuing medical education are developed, tested and approved, they, too, will be included in the Certification Program.

When the program has been fully worked out and approved, a booklet explaining it will be made available to all physicians in California. The booklet will also detail the ways in which CMA will help physicians maintain an on-going record of those educational activities which qualify him for certification.

A mechanism for the accreditation of actual con-

tinuing medical education activities is being developed by a separate committee of the CMA Scientific Board that is appointed specifically for this purpose. This Accreditation Committee is clearly differentiated from CMA's Committee on Continuing Medical Education, with the latter setting policy guides and the former charged with developing the actual mechanics of accreditation.

A second innovative program by CMA's Committee on Continuing Medical Education will catalyze the efforts of community hospitals to strengthen and improve their own staff educational activities. This program, like the Certification project, is a response to a recommendation of the 1969 Planning and Goals Conference. From that Conference emerged recommendations that the medical staff of every hospital establish an educational committee, that educational programs be developed in response to specific needs, as revealed by a systematic assessment of the quality of medical care within the hospital, that these educational efforts be properly evaluated as to effectiveness, and that CMA provide staff assistance and materials to facilitate carrying out these recommendations.

Accordingly, a CMA Continuing Medical Education Subcommittee on Evaluation is preparing materials on methods and techniques of evaluation which are relevant to this charge. They will be made available to hospitals seeking help in upgrading their staff educational activities. Through the activities of this subcommittee, a constant interchange of information will be carried out concerning new developments in the field of continuing medical education which are applicable in a hospital setting.

## Attention, Pathologists

**Mario Werner, M.D., Clinical Pathologist at Washington University School of Medicine, St. Louis, will speak at the Pathology Section meeting of the Annual Scientific Assembly, March 7. Mark your calendar.**

# LETTERS *to the Editor*

## Supermarket Medicine

*To the Editor:* The average American's love affair with his car together with a craving for convenience has spawned all kinds of roadside industries. Here in the West we can mail a letter, make a bank deposit, obtain almost any form of food from fish and chips to fried chicken, see a movie and even listen to a Sunday sermon in church all without leaving our cars. The natural center for most of this commercial attraction has become the shopping center parking lot.

It is far from uncommon to see among the popcorn stands and the fried chicken counters some form of paramedical mobile van. If the public now looks to the shopping center with almost the same confidence it used to reserve for the medical center, perhaps we are ourselves partly to blame.

It was back in the days of World War II when the recruitment of large numbers of blood donors was a national necessity that someone conceived the idea of sending specially equipped medical vans prepared to draw blood on the spot out to where people congregated. It was an effort to achieve what retailers call an impulse sale.

At about the same time what may have been over-zealous case finders dispatched well-equipped mobile chest x-ray vans hither and yon from one busy intersection to fairground to city hall courtyard, etc. The public thus became conditioned to accept medical personnel "doing their thing" in all sorts of unusual places.

Accordingly, when it seemed expedient to vaccinate vast numbers of the population as quickly as possible with the newly available Salk vaccine, the medium of the fair booth in the midway, or the mobile van, or the vacant shopping center storefront was a natural locale.

Logically, local Chambers of Commerce, recognizing a good thing when they see it, have prevailed upon local physicians to administer tetanus shots under similar field conditions.

Certainly it is time to step back and ask ourselves just where this de-emphasis of professionalism in medicine is leading us. As I pointed out above, all kinds of diagnostic vans are already commonplace. Many more can be developed. Just last week, for example, a local restaurant displayed an advertisement for a Hearmobile. How long will it be before someone discovers the commercial salability of the SMA-12 survey. Can't you see the sign, "Come in now—twelve big tests and your blood pressure checked for \$9.95. Double stamps today." Feminine modesty will probably limit Pap smears from gross exploitation but how about tonometry, electrocardiograms and even barium enemas if someone can be found to read them.

The specter of some highly advertised, chrome embellished "Doctor's Market" with its individual booths purveying the illusion of diagnosis or health to the ignorant or unsophisticated is not too far-fetched. Have you seen white-goateed "doctors" taking blood pressures along a midway? A subtle tie-in with a health foods store may not be in the patient's best interest.

How many realize that in many communities the respectable old chest x-ray van is no longer operated by your friendly neighborhood TB Association but is a privately owned commercial enterprise. Who sees to it that female patients who may be pregnant are properly protected against x-ray exposure? Who guards the neurotic from reassuring himself of good health by having an x-ray of the chest every week? Who informs the ignorant that angina doesn't show up on an x-ray and that a negative report does not mean no heart disease?

What to do about it? Certainly one giant step in the right direction is to emphasize to the public and seek legislation from government stressing that anonymous services in a parking lot are not quality medicine and that the way to receive responsible medical care is from an identifiable physician, be he in a private office, health department or clinic.

ARTHUR D. SILK, M.D.



# Whither Nursing?

*To the Editor:* At a recent meeting of the California Nurses' Association Board of Directors, there was discussion of your editorial, in the December issue of CALIFORNIA MEDICINE.

The CNA Board of Directors found your editorial interesting and provocative. They noted your statements: "The varieties of nurse specialists are growing . . ." [and] "nurses are being expected to make independent decisions. . . ." "One important and perhaps inevitable result . . . is that the nurse . . . has begun to stand more closely with the physician as an assistant, associate or even colleague." "We see nursing leadership making very considerable efforts to identify and define what is now to be the role of nursing." And, "Perhaps the time has come to admit that the specialized registered nurse of today and tomorrow will no longer be a nurse in the traditional sense, and will more than likely be lifted out of the traditional nursing role to take her place among a new order of physician assistants or physician associates." "The need for such an order . . . with various and differing skills is becoming increasingly apparent." And further, "This new category of professional specialists should stand closely with the physician and share his responsibilities for patient care and for community, environmental and species health care. Men would play an equal role with women. Those who achieved this new status might become recognized as 'professional associates in medicine' . . ."

The CNA Board of Directors appreciates your insight and thoughtful review of the problems of the expanding role of the nurse.

At the same meeting, action was taken to adopt a CNA Position on the Expanding Role of the Nurse. [See below.]

MRS. A. LIONNE CONTA  
*Executive Director*

## CNA Position on the Expanding Role of the Nurse

The CNA recognizes that health needs arise from a variety of social, cultural and economic as well as physical cases; that changes brought about by scientific and technological discoveries are necessitating new and different methods and practices in the delivery of health

care; and that legislative action reflecting public policy have emphasized the increased demand for health services.

The CNA further acknowledges that the nursing profession must assume responsibility for defining the dimensions of services that can and should be provided by nurses.

The CNA structure provides for participation by nurses in all fields of practice. Interorganizational representation already established provides for cooperative work with related health professions.

Therefore the CNA will urge, promote and encourage defining the expanding role of the nurse, determining adequate preparation and job assignment, and full exploration of added professional and legal responsibility.

*Adopted by Board of Directors, CNA, December 6, 1969.*

## Peer Review

*To the Editor:* "Peer Review" has been a favorite phrase that recurs in the emanations from various echelons of organized medicine and seems to be highly touted as a remedy for a number of ills that beset medical practice. Like many popular remedies, however, the original bloom of the manufacturer's enthusiasm is eventually dimmed somewhat with the reporting of undesirable side reactions. From what I read, it seems to me that the peer review enthusiasts haven't been reading the package inserts.

I recently had the opportunity to observe the operation of the peer review concept in the form of an inspection of the hospital where I have been practicing for almost twenty years by none less than the Joint Commission on Accreditation. If this is peer review at its best and will cure what's wrong with the patient, I regret to report that it also causes more than a modicum of trauma, tenesmus and tetany in the process. Although this is only a preliminary report to your readers, perhaps some of them have made similar observations and hopefully it may prompt further investigation by suitable committees of CMA.

The paper tiger that inspected us seemed convinced that the only good doctor is a literary one and that a voluminous history full of minutiae guarantees the excellence of the attending physician. That such a notion is patently false must be apparent to anyone who actually handles patients. This obsessive neurosis regarding charts becomes manifest every time their inspector appears and the last such display of papyrophilia was a temper tantrum about family histories in our charts. Sure-

ly, until some genius reports on the genetic implications of hemorrhoids, couldn't we leave it up to the attending physician as to whether such data should be included? Yet, the Commission is adamant and I know of major league umpires that have less rigid concepts than the Commission.

Our general practice section was especially affected by the "cure." Their own meetings, which were not evaluated, were summarily dismissed as being inadequate "for credit." They can only acquire learning in another section, according to the Commission's edict, apparently on the old theory that the only way to feed sparrows is by feeding horses. Now, the generalist can listen to a lecture in the surgical section meeting and "get credit" while if the same surgeon gives the same lecture in the same room at a GP meeting, it doesn't count. This denigration of the generalist comes at a time when there seems to be a general acceptance of his importance as a family doctor in American medicine.

Another ultimatum affecting our practice is the development of a structure of profiles on each doctor which will supposedly prevent a physician from attempting unfamiliar procedures. The delicate matter of privileges had already been worked out by our staff but that system was scrapped by the Commission without evaluation. Any attempt at originality or innovation that doesn't comply is apparently squelched from the infallible Olympian Heights in Chicago.

All this might have been good-naturedly tolerated but since Medicare, hospital payments will be denied unless the hospital has Commission approval. With such newly acquired puissance, the Commission's suggestions become edicts and their opinions ultimatums. Taxpayer patients who built our hospital may be denied the benefits of Medicare because of the capricious decisions of a Commission that has no insights into the medical needs of the community. This seems to be very close to the "restraint of trade problem" that plagued the AMA in the thirties and at any rate appropriate legal countermeasures can reasonably be expected any day.

No one doubts the motives of the Commission and it would seem that our staff should enjoy a reciprocal opinion from the Commission. Instead, the Commission seems to fear and distrust doctors generally. Perhaps this iatrophobia is more apparent than real. Perhaps we just drew a catankerous inspector whose jaundiced and crapulous mien

doesn't reflect the attitude of the Commission. However, the fatuous nitpicking, niggling, cavilling and inane regulations have served to increase the secretarial burden of the hospital, interfere with the care of patients and add to skyrocketing costs. One wonders at the response that this fiasco would have evoked, if it were enacted by a government agency. As it is, it has hardly improved professional solidarity and the term "peer review" has acquired new unsavory connotations to many members of our staff. Is this operation the will of doctors generally? How long will these buffoons continue to abuse our patience?

Several years ago, a wag in our County Medical Society, calling himself Phil O. Sofer, Jr., wrote a verse about all this which I repeat below. Maybe peer review will take its real place in our therapeutic armamentarium when we all appreciate its virtues *and* dangers.

ALF T. HAEREM, M.D.

## THE ODD AUDIT BIRD

(Tune: Tit Willow)

*On a spreading Sequoia, an audit bird lit  
Singing, "Audit! I'll Audit! I'll Audit!"  
And I said, "Little Audit Bird, why do you sit  
Singing 'Audit, I'll Audit, I'll Audit!' "  
"Is it iatrophobia, Birdie?" I cried,  
"Or a drive for reform in your little inside?"  
"Oh, my motives are purer than snow!" he replied,  
Adding, "Audit, I'll Audit, I'll Audit!"*

*For this virtuous bird with the scholarly plume,  
Singing, "Audit! I'll Audit! I'll Audit!"  
Was convinced that all others should sing the same  
tune  
And sing, "Audit, I'll Audit, I'll Audit!"  
Messianic in fervor, he brooked no revolt;  
For the bird with less plume was considered a dolt,  
Whom he thought he could show how to sing and  
to moult  
With his "Audit! I'll Audit! I'll Audit!"*

*Now the song and the plume are ordained at the  
hatch;  
Not by "Audit, I'll Audit! I'll Audit!"  
And you only can change it by starting from scratch,  
Not by "Audit! I'll Audit! I'll Audit!"  
For the value of song will be hard to assess  
By the meager criteria you may possess;  
Maybe singing together might be a success —  
Without "Audit! I'll Audit! I'll Audit!"*

# PUBLIC HEALTH REPORT

Louis F. Saylor, M.D., M.P.H., Director, State Department of Public Health

## Hemolytic Disease Of the Newborn

### A New Law for Prenatal Blood Test and Disease Reporting

IN 1968 RH IMMUNE GLOBULIN was licensed and became commercially available. It offers Rh-negative women the means for preventing maternal Rh isoimmunization and hemolytic disease of the newborn (HDN) in their subsequent pregnancies. At present, HDN accounts for 3 percent of California's perinatal mortality, accounting directly for more than 1,600 deaths in the last five years. Estimates of the total morbidity from HDN range from 1,000 to 2,000 cases a year, with some of the patients having serious continuing disabilities as a result. A partial measure of this morbidity is found in the 108 patients in state institutions with mental retardation due to HDN. In addition to the personal and family tragedy involved, the annual cost for the care of these patients alone is \$648,000 a year. It is clear that the human and economic costs of the disease make the effective use of the new agent an urgent medical issue.

In California, there are an estimated 51,000 non-sensitized Rh-negative women terminating pregnancy each year, and ideally, nearly all will receive Rh Immune Globulin. If such a preventive program is consistently carried out, the immunization will eventually save 400 infant lives a year in California, as well as prevent the disability and family burdens that often accompany the disease. However, some difficulties can be expected because Rh Immune Globulin has unique and demanding characteristics. Specifically, (1) it must be administered *after each pregnancy*, (2) the time element is uncompromising (it must be given within 72 hours after termination of pregnancy), (3) it is still relatively expensive, (4) it is used as an integral part of the physician's management of an individual patient, and is not amenable to use in public or mass programs.

With these points in mind, last year the Legislature passed a bill (AB 2026) authored by Mr.

MacDonald (D-Ventura) to provide a means for control and surveillance of HDN. The law has three basic features. One is that blood typing be done (or known) for all prospective mothers, a recommended standard for prenatal care for many years. The second is that the woman be informed of the results of the blood typing. The third is that all cases of HDN be reported.

The blood typing and informing of the mother are clearly elements pertaining to the physician and the clinic or hospital in which he practices. The implications of the legislation call for a review and strengthening of procedures to assure that women who are Rh negative are identified, the primary step toward effective use of the immune globulin. The third requirement pertains to both the private and public sectors and asks for reporting of HDN to the California Department of Public Health. This will allow an assessment of the problems and impact of the new immunization.

A preliminary survey by this department has already identified some areas of difficulty in an effective preventive program. It was found that a number of women were refusing the immunization because they did not intend to have additional children. Because contraceptive failures occur and intentions regarding pregnancy change, this reason for refusal may prove to be faulty. Other reasons for refusal were religious beliefs and inability to pay. Since its introduction, the cost of the product has been reduced from \$64 to \$30 at this writing, and refusals due to cost have probably been decreased as well. Moreover, many blood banks stock the Rh Immune Globulin and will exchange it for a blood donation. The survey, which did not include the entire state, also identified two hospitals which had not stocked the product.

As surveillance of HDN is achieved, the progress and trend data from the reports will be presented to the medical profession. If significant areas of breakdown in preventive measures are identified, they will be noted so corrective action can be taken. We now have an opportunity to virtually eliminate the problem of hemolytic disease of the newborn in the next decade. The cooperation and diligence of physicians, hospitals and laboratories will be the essential elements for the success of this effort.



## Information

### Use of Anti-Arrhythmic Agents Other Than Digitalis

LEONARD S. DREIFUS, M.D.

*Material Supplied by the California Heart Association*

**Quinidine.** The current therapeutic status of quinidine has changed little since Wenckebach's classic observations on recurrent atrial fibrillation. Although many antiarrhythmic agents have appeared on the pharmacologic horizon, none has surpassed the efficacy of quinidine, an agent effective in any active arrhythmia, whether atrial, A-V nodal or ventricular. The introduction of precordial electroshock therapy by Zoll and his associates and Lown has imparted a new dimension in the approach to antiarrhythmic therapy and made it possible to convert almost 90 percent of the patients with atrial fibrillation to sinus rhythm. Nevertheless, the usefulness of quinidine has not diminished because a pharmacologic program must be instituted to maintain a sinus rhythm even after electro-conversion.

The usual drug method of converting atrial fibrillation to sinus rhythm in the digitalized patient is to administer quinidine in a dosage of 0.2 gm every two hours for five doses the first day; 0.3 gm every two hours for five doses the second day; 0.4 gm every two hours for five doses the third day; and so forth. If conversion fails at 0.6 gm (total daily dose of 3.0), the likelihood of conversion is small and the maintenance of sinus rhythm is probably not feasible. Higher doses are attended

with toxicity, quinidine syncope, and cardiac standstill. Although quinidine may be useful in converting atrial flutter, the drug should not be used to convert atrial flutter with 2:1 A-V conduction ratio without previous digitalization, since the vagolytic effects of quinidine may allow 1:1 A-V conduction to occur with a dangerously rapid ventricular rate. Quinidine may be administered in a dose of 0.2 to 0.4 gm three to four times a day to control ventricular or atrial premature systoles. Quinidine may be effective in the treatment of arrhythmias associated with Wolff-Parkinson-White syndrome and occasionally it may abolish the electrocardiographic changes of this syndrome. The combination of a small dose of quinidine 100 to 200 mg four times a day with propranolol 10 to 20 mg four times a day has proved extremely effective in controlling Wolff-Parkinson-White tachycardia, recurrent atrial flutter or fibrillation and in the presence of intermittent ventricular tachycardia.

Although it has been traditionally recommended that a test of quinidine be given to elicit idiosyncrasy, many clinicians utilize the first dose of a therapeutic program for this purpose.

Toxicity may be manifested by pulmonary, gastrointestinal, or cardiac signs and symptoms. Cyanosis, respiratory depression, vascular collapse, restlessness, pallor, cold sweat and syncope are not uncommon. Cinchonism may develop, with tinnitus, vertigo, visual disturbances, headache, confusion, angioneurotic edema, nausea, vomiting, diarrhea, fever or cutaneous manifestations. Thrombocytopenia has been observed occasionally and may be associated with a grave prognosis.

A widening of the QRS complex of more than 25 percent is a warning of impending toxicity and the drug should be discontinued. Cardiotoxicity may be successfully antagonized by 40 to 80 mEq molar sodium bicarbonate or 1 to 3 micrograms per minute of isoproterenol.

**Procainamide.** More than 40 years ago, it was found that procaine could paralyze extracardiac nerves; but, because of rapid hydrolysis, therapeutic levels were difficult to maintain and it never became a clinically useful antiarrhythmic drug. On the other hand, procainamide which binds para-aminobenzoic acid and diethylaminoethanol through an NH group is not affected by the choline esterase of the body and consequently is effective by the oral and parenteral routes with a more prolonged duration of action.

Dr. Dreifus is from the Department of Medicine, Hahnemann Medical College, Philadelphia, Pennsylvania.

The hemodynamic effects of procainamide are not unlike quinidine. However, large doses of intravenous procainamide may cause serious hemodynamic derangements.

Although it was originally thought that procainamide depressed contractility of cardiac muscle less than quinidine, more recent studies suggest that equivalent doses expressed as milligrams per kilogram depress cardiac muscle equally.

As in the use of quinidine, it is important to realize that patients with renal damage or with congestive heart failure excrete procainamide more slowly than do normal persons, and cumulative effects are a potential danger. Procainamide, like quinidine, acts on the atrium and ventricle by increasing the refractory period and conduction time and has anticholinergic effects on the atria and A-V node. The electrophysiologic effects of the drug are similar to those of quinidine. However, these similarities do not adequately explain the successful use of one drug when the other has failed as an antiarrhythmic agent.

Although procainamide is probably less successful than quinidine in reverting atrial fibrillation to sinus rhythm, it has been used in quinidine-sensitive patients. Likewise, it has been effective in restoring sinus rhythm in patients with atrial flutter and atrial tachycardia. Procainamide appears to have a distinct advantage over quinidine in the management of ventricular tachycardia, when urgent intravenous therapy is required. The rate of intravenous administration should not exceed 100 mg per minute, and electrocardiographic monitoring is imperative during the period of injection. We have frequently and successfully treated atrial tachycardia with block and ventricular tachycardia, with procainamide in the presence of digitalis overdosage. However, the management of ventricular or junctional tachycardia in high grade A-V block requires special attention. Depressant agents, such as quinidine, procainamide and potassium salts may abolish all subsidiary pacemakers and engender cardiac standstill. Hence, electrical pacing or isoproterenol are best utilized in this clinical setting.

The toxic signs of procainamide include hypersensitivity reactions such as skin eruptions, bone marrow depression or lupus erythematosus with proteinuria and polyserositis. The development of hypotension or widening of the QRS complex beyond 25 percent of control is a definite indication to withdraw this agent. As in the use of quinidine,

infusion of hypertonic sodium salts will reverse procainamide toxicity.

**Lidocaine.** The pharmacologic activity and electrophysiologic mechanisms of lidocaine are similar to those of quinidine and procainamide. It has proved extremely effective in terminating ventricular tachycardia, especially in the presence of an acute myocardial infarction and premature ventricular systoles.

The main hallmark of this agent is its superiority to procainamide in certain specific situations when a short-acting agent is required, particularly in hearts previously depressed by other antiarrhythmic agents or where only a transitory antiarrhythmic effect is indicated. It has been used successfully in depressed hearts following open heart surgery to control ventricular tachycardia before the termination of extracorporeal circulation. However, it is impractical for the very long term treatment or prevention of paroxysmal ventricular tachycardia. It is safe and effective in a single intravenous dose of 1 mg per kilogram with repeated doses every 20 minutes to a maximum of 750 mg. Usually a bolus injection of 50 to 100 mg is administered intravenously, followed by an intravenous drip of 2 to 4 mg per minute to prevent the reappearance of ventricular premature systoles. This agent has significantly reduced the mortality associated with ventricular tachycardia and fibrillation in the presence of an acute myocardial infarction and has become the most useful antiarrhythmic agent in the coronary care unit. Similar restrictions as stated under quinidine and procaine should be observed in the presence of high grade A-V block.

**Diphenylhydantoin.** Diphenylhydantoin (Dilantin®) appears equally effective in both supra-ventricular and ventricular arrhythmias and possesses properties which make it effective against digitalis-induced arrhythmias. It has been successful in preventing paroxysmal atrial tachycardia (PAT) when the usually employed antiarrhythmic agents have failed. It has proved effective in suppressing atrial, A-V nodal, and ventricular premature systoles, and is particularly effective in terminating digitalis-induced arrhythmias. Its transient action and rapid reversibility of toxic effects may give it certain advantages over other depressant agents. However, it does not appear effective in converting atrial fibrillation to sinus rhythm. In the treatment of rapid supraventricular or ventricular tachycardias, 5 to 10 mg per kilogram can be slowly injected intravenously over a 15-minute



period and repeated within two to three hours. The drug can be administered orally, from 100 to 200 mg four times daily, for the suppression of ectopic beats or prophylaxis against recurrent paroxysmal tachycardia.

Toxic manifestations of diphenylhydantoin are seen in approximately 10 to 15 percent of patients and include nervousness, ataxia, tremors, nystagmus, visual disturbances, respiratory arrest, confusion or drowsiness, gastric distress, erythematous or morbilliform cutaneous eruptions and hyperplasia of the gums.

**Beta Adrenergic Blocking Agents.** Interest in blocking the effects of adrenergic nerve stimuli is attributed to Dale who, in 1906, described the reversal of the pressor response to epinephrine by pretreating experimental animals with certain ergot compounds. Ahlquist recognized two types of adrenergic receptors and designated these alpha and beta.

Propranolol reduces the heart rate and cardiac contractile force. Arterial pressure and ascending aortic flow are slightly reduced in anesthetized dogs. As these changes do not occur after depletion of norepinephrine stores by syrosingopine, it is concluded that they result from blockade of resting sympathetic drive. In humans, administration of propranolol will cause a decrease in cardiac output and left ventricular work at rest and during exercise. Propranolol will abolish the vasodilation effects of epinephrine and isoproterenol but not the vasoconstrictor effects of the catecholamines on the peripheral vessels.

With intravenous administration, propranolol exerts a rapid antiarrhythmic action. Propranolol is usually given slowly in doses of 1 to 5 mg intravenously (no more than 1 mg every two or three minutes) or 15 to 30 mg three to four times daily may be given by the oral route prophylactically to prevent the return of ectopic beating. The action is usually immediate during the intravenous administration and the drug may be repeated within two to three hours.

The side effects of propranolol may include lightheadedness, drowsiness, nausea, diarrhea, sleeplessness, rashes, visual disturbances, purpura, paresthesias, flushing, and mental confusion. The pharmacologic effects of propranolol have produced hypotension, bradycardia, cardiac failure, A-V heart block, bronchial wheezing and aggravation of mild obstructive pulmonary disease.

## Current Status of Multiphasic Screening

CMA HOUSE OF DELEGATES, Resolution No. 37-69 calls for the profession to be kept informed of progress and development in the field of multiphasic screening. It also asks that appropriate component parts of multiphasic screening be defined. Since the adoption of this resolution, the need for information has increased. Multiphasic screening has become big business with major organizations promoting programs for hospitals, medical societies, union groups, retirement communities, etc. The CMA Council has given the responsibility for following developments in this field to the Commission on Community Health Services. The following is the commission's report as of this time.

Unfortunately it is not yet clear just what part multiphasic screening should properly play in health care. Nor is it possible to delineate the appropriate components of a multiphasic screening program with any precision. Therefore, this report can only raise some of the critical questions which we feel must be answered.

Programs for large populations are being promoted on the basis that they will provide early detection and/or prevention of disease. Certainly the objective cannot be questioned. However, there is little concrete evidence that the method accomplishes the objective. A large group is surveyed and the proponents report that 40 percent have been found to have positive findings. Evaluation of the significance of such positive findings must be critically examined. There is virtually no meaning in merely reporting that so many cases of a given condition were discovered as the result of a mass survey of so many people, unless it can also be demonstrated that the existence of the condition was unknown either to the patient or to his physician. Furthermore, unless it can be shown that detection of the condition materially affects the prognosis there is little value in detection per se.



In reporting "positive findings" no effort has been made by the proponents to screen out what might be no more than false positive laboratory findings. The raw data resulting from the Cannery Workers' program suggest that when proper follow-up is done and these factors considered the yield of truly significant findings may be remarkably small. However, the data in question has not yet been adequately studied to justify firm conclusions. Application for a research grant has been submitted which would make possible complete follow-up of the individuals tested and thorough analysis of the data. California Medical Association has cooperated with the Cannery Workers' program in the past and continues to do so. County medical societies have been urged to arrange follow-up of "positive findings" by competent local physicians and should try to cooperate with the research project if it develops.

In evaluating the yield of multiphasic screening programs each component, of course, must be studied individually. The overall program and the individual components must be assessed in

terms of cost as well as yield. Again the statements of the proponents that it costs \$40 or \$50 or \$60 to screen an individual has little meaning. The cost of the follow-up studies must also be included and then assessed against the useful yield. It is quite likely that the cost of follow-up will prove to be considerably more than the cost of the original screening and this possibility should certainly be pointed out to groups considering such a program.

Since critical questions remain unanswered, the Commission on Community Health Services recommends that component societies and individual physicians continue an expectant attitude toward multiphasic screening. Concerned organizations and the general public should feel that the profession is available for advice. At this time we believe programs should be limited as to the number of people included and to those few components which, in professional judgment, are most likely to be of value.

MARVIN J. SHAPIRO, M.D.  
*Chairman, Commission on  
Community Health Services*

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# California Medical Association



## Council Highlights

Highlights of the Actions of the California Medical Association  
Council Meetings, September 27 to 28, Los Angeles, and  
November 21 to 22, Los Angeles

*This summary is published so that CMA membership may be advised in brief of the actions of the Association's Council. It covers only major actions and is not intended as a detailed report. Full minutes of these meetings are available upon any member's request to the CMA office.*

### 557th Meeting, September 27 to 28, 1969 Los Angeles

Possible formation of a physician-owned or controlled professional liability carrier will be studied by an independent consultant for CMA. A statewide study of the entire liability problem, including the reasonableness of current insurance premium rates, with special reference to forming some type of carrier was recommended by the CMA Medical Review and Advisory Committee and approved in principle.

Other recommendations aimed at alleviating the medical liability crisis approved by Council were:

- Initiate an immediate and extensive effort to encourage additional established and reputable insurance carriers to provide physicians professional liability insurance coverage in California.
- Sponsor a pilot project to test medical/legal screening panels in selected counties. Joint committees would be patterned after already successful panels in Arizona, Nevada and New Mexico.
- Seek the cooperation of insurance carriers, and others interested in personal injury awards, in developing and obtaining appropriate legislation regarding "measure of damages."

- Continue to inform legislators about the medical liability problem confronting physicians; develop and pursue passage of appropriate legislation.

- Designate the CMA Medical Review and Advisory Committee as CMA's liaison to professional liability carriers; encourage carriers to use MRAC services as a consultant as needed.

(Some medical societies already have effective liaison with professional liability carriers.)

- Endorse the newly-formed Medical Executives Conference Liaison Committee to the CMA Medical Review and Advisory Committee.

(The new liaison committee is valuable as a further access to opinions and recommendations from component medical societies.)

- Encourage county medical societies to continue—at the local level—to seek solutions to the medical liability problem; urge societies to conduct malpractice prevention workshops, in cooperation with local hospitals and medical staffs, tailored to respond to local needs.

A recommendation to contract with the Department of Rehabilitation regarding peer review for medical services under the McAteer Alcoholism Program was approved.

**A position paper on smoking and health** was approved. The paper prepared by the California Interagency Council on Smoking and Health has eight recommendations, seven of which were supported by the Council.

**New CMA Councilor** is Dan W. Clark, M.D., San Jose, elected to fill the unexpired term of Richard S. Wilbur, M.D., Santa Clara, who has resigned. Doctor Clark will represent the Seventh District which covers the counties of Monterey, San Benito, San Mateo, Santa Clara and Santa Cruz.

**558th Meeting, November 21 to 22, 1969**  
Los Angeles

**CMA support of the Health Facilities Bond Act (AB 1073)** was reaffirmed by CMA Councilors at their final meeting of the year. The bond measure, which goes before the state's voters in the June 2 primary election in 1970, would provide \$246,300,000 for the construction of health science facilities on University of California campuses. CMA Council was one of the first organizations to support the measure.

**The concept of "Universal" Health Care Coverage** was approved. The Council recommendation states that "CMA should support the concept of 'universal' health care coverage utilizing multiple methods of financing and free choice of mechanism based on adequate standards of coverage." Implicit in the concept is the recognition that the federal government would be responsible for the financing of comprehensive health care for the economically deprived. By "universal," the Council means a pluralistic system making health insurance automatically available to all persons. It would be designed to utilize multiple organizational approaches (AMA's current "MediCredit" proposal to Congress represents one such approach).

**A recommendation to set up a Coordinating Council for Health Standards and Licensure** for new professional groups was endorsed. The recommendation will be submitted to the next session of the Legislature. The proposed council, according to the recommendation, consists of the follow-

ing members: five physicians, five licentiates (dentists, nurses, veterinarians), two consumers and three hospital administrators and educators.

**A statewide rubella vaccination plan** to determine the effectiveness of the state's rubella vaccination program was endorsed. The State Department of Public Health, in cooperation with local health departments, is coordinating the plan in which all physicians are urged to participate.

**Establishment of a committee to review the size of the CMA House of Delegates and Council** was approved. The committee will report back to the Council with recommendations for the 1971 House of Delegates.

**Proposed principles, goals and methods for the Peer Review Survey Program** of extended care facilities were approved. The proposed program was developed by the CMA Committee on Long-Term Care Facilities.

**A proposed CMA Continuing Education Plan** based upon awarding physicians certificates for completing a minimum number of hours was accepted. The basic format for such an education plan was developed by the CMA Committee on Continuing Medical Education. The plan will be presented to the 1970 CMA House of Delegates meeting next March in San Francisco. The plan was prepared in response to a 1969 CMA House of Delegates resolution calling for Council to make available to all practicing physicians in California the specific administrative mechanism "to collect, codify and certify participation in accredited postgraduate instruction."

**The creation of a large-scale program** to study and research ways to improve methods of delivering health care was approved.

**Formation of an ad hoc Task Force on Medi-Cal Improvements** to prepare recommendations concerning CMA's legislative program in this crucial area was approved.

Councilors accepted the nomination of Frederick Ackerman, M.D., Pleasant Hill, as CMA Councilor to replace William F. Kaiser, M.D., Berkeley, who has resigned. Doctor Ackerman will be in Office No. 2 of the Ninth District covering Alameda and Contra Costa counties.



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# In Memoriam

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Persons wishing to do so may make contributions to the Physicians' Benevolence Fund to honor the memory of a member who has died. Members of the family will be notified that such a contribution has been made and the name of the donor will be supplied.

Checks should be addressed to Physicians' Benevolence Fund, Inc., California Medical Association, 693 Sutter Street, San Francisco, Ca. 94102.

ALLEN, JOHN H., Placentia. Died 4 December 1969 in Fullerton, aged 43. Graduate of Marquette University School of Medicine, Milwaukee, 1954. Licensed in California in 1956. Doctor Allen was a member of the Orange County Medical Association.

ARNOLD, HARRY JOSEPH, San Jose. Died 3 May of osteitis deformans, aged 68. Graduate of The Creighton University School of Medicine, Omaha, 1925. Licensed in California in 1926. Doctor Arnold was a retired member of the Santa Clara County Medical Society and the California Medical Association, and an associate member of the American Medical Association.

CASTELHUN, PAUL, San Francisco. Died 16 December 1969 in San Francisco of asphyxiation in a fire at his home, aged 91. Graduate of the University of California School of Medicine, Berkeley-San Francisco, 1904. Licensed in California in 1905. Doctor Castelhun was a member of the San Francisco Medical Society.

HARRIS, MAXWELL J., Burlingame. Died 5 August 1969 in South Lake Tahoe of coronary artery insufficiency due to arteriosclerosis, aged 63. Graduate of the University of Nebraska College of Medicine, Omaha, 1935. Licensed in California in 1942. Doctor Harris was a member of the San Mateo County Medical Society.

LAMB, HOWARD E., Apple Valley. Died in November 1969 in Utah of carcinoma, aged 74. Graduate of the American School of Osteopathy, Kirksville, Missouri, 1917. Licensed in California in 1933. M.D. degree from California College of Medicine, 1962. Doctor Lamb was a member of the San Bernardino County Medical Society.

LEWIN, LUC, Hawthorne. Died 19 December 1969 in Hawthorne of myocardial infarction, aged 61. Graduate of Schlesische Friedrich-Wilhelms-Universität Medizinische Fakultät, Breslau, Prussia, 1936. Licensed in California in 1949. Doctor Lewin was a member of the Los Angeles County Medical Association.

LITTLE, SHERMAN, Los Angeles. Died 15 November 1969 in London of heart disease, aged 62. Graduate of Yale University School of Medicine, New Haven, 1933.

Licensed in California in 1959. Doctor Little was a member of the Los Angeles County Medical Association.

LYNE, WALTER C., San Mateo. Died 8 December 1969 in Hillsborough, aged 64. Graduate of Stanford University School of Medicine, Palo Alto-San Francisco, 1947. Licensed in California in 1947. Doctor Lyne was a member of the San Mateo County Medical Society.

MINTZER, SIDNEY, Granada Hills. Died 5 December 1969 in Van Nuys of burns received in a fire, aged 54. Graduate of The Chicago Medical School, 1947. Licensed in California in 1954. Doctor Mintzer was a member of the Los Angeles County Medical Association.

NIELSEN, JOHANNES M., Los Angeles. Died 12 December 1969 in Los Angeles of cerebral thrombosis, aged 79. Graduate of the University of Illinois College of Medicine, Chicago, 1924. Licensed in California in 1929. Doctor Nielsen was a member of the Los Angeles County Medical Association.

OWEN, ETHEL DALE, Aptos. Died 12 December 1969 in Santa Cruz of heart disease, aged 79. Graduate of Stanford University School of Medicine, Palo Alto-San Francisco, 1917. Licensed in California in 1917. Doctor Owen was a retired member of the San Francisco Medical Society and the California Medical Association, and an associate member of the American Medical Association.

POIRIER, KURT PETER (K. Peter), Sacramento. Died 24 November 1969 in Sacramento, aged 49. Graduate of Ludwig-Maximilians-Universität Medizinische Fakultät, München, Bavaria, 1949. Licensed in California in 1957. Doctor Poirier was a member of the Sacramento County Medical Society.

RADFORD, EDWARD BERTRAM, Walnut Creek. Died 23 November 1969 in Orinda of pulmonary emphysema, aged 70. Graduate of Northwestern University Medical School, Chicago, 1931. Licensed in California in 1931. Doctor Radford was a retired member of the Alameda-Contra Costa Medical Association and the California Medical Association, and an associate member of the American Medical Association.

REINARTZ, EUGEN G., Carmel Valley. Died 29 July 1969 in Fort Ord of coronary artery occlusion and myocardial infarction, aged 79. Graduate of Medico-Chirurgical College of Philadelphia, Pennsylvania, 1916. Licensed in California in 1920. Doctor Reinartz was a retired member of the Monterey County Medical Society and the California Medical Association, and an associate member of the American Medical Association.

REISS, BERTRAM, San Fernando. Died 26 November 1969 in Los Angeles of malignant lymphoma, aged 40.

Graduate of College of Osteopathic Physicians and Surgeons, Los Angeles, 1955. Licensed in California in 1956. M.D. degree from California College of Medicine, 1962. Doctor Reiss was a member of the Los Angeles County Medical Association.



SHEPARD, RICHARD JOSEPH, Tarzana. Died 30 November 1969 in Tarzana of heart disease, aged 54. Graduate of College of Osteopathic Physicians and Surgeons, Los Angeles, 1942. Licensed in California in 1942. M.D. degree from California College of Medicine, 1962. Doctor Shepard was a member of the Los Angeles County Medical Association.



SOOY, JOSEPH W., Napa. Died 17 December 1969 in Napa, aged 73. Graduate of Yale University School of Medicine, New Haven, 1926. Licensed in California in 1930. Doctor Sooy was a retired member of the Napa County Medical Society and the California Medical Association, and an associate member of the American Medical Association.

SPEARS, RALPH G., Northridge. Died 8 December 1969 in Northridge of aneurysm of the aorta, aged 48. Graduate of Northwestern University Medical School, Chicago, 1951. Licensed in California in 1961. Doctor Spears was a member of the Los Angeles County Medical Association.



WALKER, R. JAMES, Oakland. Died 28 November 1969 in Oakland of coronary occlusion, aged 62. Graduate of Stanford University School of Medicine, Palo Alto-San Francisco, 1933. Licensed in California in 1933. Doctor Walker was a member of the Alameda-Contra Costa Medical Association.



WALSH, FREDERICK M., Long Beach. Died 7 December 1969 in Los Angeles of cerebral vascular disease, aged 57. Graduate of the University of Manitoba Faculty of Medicine, Winnipeg, 1945. Licensed in California in 1951. Doctor Walsh was a member of the Los Angeles County Medical Association.

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# CONTINUING EDUCATION ACTIVITIES IN CALIFORNIA AND HAWAII (FORMERLY WHAT GOES ON)

## COMMITTEE ON CONTINUING MEDICAL EDUCATION

THIS BULLETIN of information regarding continuing education programs and meetings of various medical organizations in California and Hawaii is supplied by the Committee on Continuing Medical Education of the California Medical Association. In order that they may be listed here, please send communications relating to your future meetings or postgraduate courses to Committee on Continuing Medical Education, California Medical Association, 693 Sutter Street, San Francisco 94102; or phone: (415) 776-9400, extension 241.

### ADOLESCENT MEDICINE

March 14-15 — **The Troubled Adolescent in Modern Family.** UCSF at Preston Hall, Mendocino. Saturday-Sunday. \$15. 10½ hrs.

### CANCER

February 21-25—**Current Concepts in Cancer Chemotherapy.** UCLA at El Mirador Hotel, Palm Springs. Saturday-Wednesday. \$125. 13½ hrs.

May 15-16 — **Hormones and Neoplasms—Cancer Conference.** USC at Century Plaza Hotel, Los Angeles. Friday-Saturday. 12 hrs.

### COMMUNITY MEDICINE

February 28—**Problems in Social Change Reflected in Medical Practice.** UCSF at Herrick Memorial Hospital, Oakland. Saturday. \$10. 6 hrs.

March 23-26—**The Urban Scene.** American Orthopsychiatric Association at Mark Hopkins and Fairmont Hotels, San Francisco. Monday-Thursday. Delivery of health care services, racism, hunger, dilemmas in welfare and education, law and order, long range urban planning, children designated delinquents, black adolescents, perinatal factors and development, natural history of brain dysfunction, psychological considerations of transplants in children. \$25 for non-members. Contact: Marion F. Langer, Ph.D., AOA, 1790 Broadway, New York 10019. (212) 586-5690.

### MEDICINE

February 17-18—**American College of Physicians — Hawaii Regional Meeting.** Pacific Club, Honolulu. Tuesday-Wednesday. Tuesday and Wednesday a.m.: Scientific Sessions. Tuesday p.m.: Lecture in connection with The American College of Surgeons, "What's Left in Thyroid Disease for the Surgeon?" 8 hrs. Contact: Morton E. Berk, M.D., Governor, Hawaii Region,

ACP, 1133 Punchbowl Street, Honolulu 96813. (808) 537-2211.

February 18—**Coronary Heart Disease, 1970.** USC at Huntington-Sheraton Hotel, Pasadena. Wednesday 9-4:30. Latest research and clinical information on diagnosis and management of coronary disease. Prevention and post-coronary rehabilitation. \$35. 6 hrs.

February 20-21—**American College of Physicians — Southern California Regional Meeting.** Coronado. Friday-Saturday. Contact: Eugene Braunwald, M.D., Chairman of Scientific Program, UCSD.

February 28-March 1—**Your Patient with Renal Disease.** UCSF at Franklin Hospital, San Francisco. Saturday-Sunday. Office recognition and evaluation, recurrent urinary tract infections, hypertension, current vascular surgical concepts in reno-vascular hypertension, urological aspects, acute and chronic renal failure, chronic hemodialysis, the community dialysis unit. \$40. 8½ hrs.

## KEY TO ABBREVIATIONS AND SYMBOLS

Medical Centers and CMA Contacts  
for Information

- CMA:** California Medical Association  
Contact: Continuing Medical Education, California Medical Association, 693 Sutter Street, San Francisco 94102. (415) 776-9400, ext. 241.
- LLU:** Loma Linda University  
Contact: John E. Peterson, M.D., Associate Dean for Research Affairs, Loma Linda University School of Medicine, Loma Linda 92354. (714) 796-7311.
- PMC:** Pacific Medical Center  
Contact: Arthur Selzer, M.D., Chairman, Education Committee, Pacific Medical Center, Clay and Webster Streets, San Francisco 94115. (415) 931-8000.
- STAN:** Stanford University  
Contact: Thomas A. Gonda, M.D., Associate Dean, Stanford University School of Medicine, 300 Pasteur Drive, Stanford 94305. (415) 321-1200, ext. 5371.
- UCD:** University of California, Davis  
Contact: George H. Lowrey, M.D., Professor and Chairman, Department of Postgraduate Medicine, University of California, Davis, School of Medicine, Davis 95616. (916) 752-0331.
- UCI:** University of California — California College of Medicine, Irvine  
Contact: Robert Combs, M.D., Associate Dean, University of California, Irvine—California College of Medicine, Irvine 92664. (714) 838-5991.
- UCLA:** University of California, Los Angeles  
Contact: Donald Brayton, M.D., Associate Dean and Head, Continuing Education in Medicine and the Health Sciences, 15-39 Rehabilitation Center, UCLA Center for the Health Sciences, Los Angeles 90024. (213) 825-6514.
- UCSD:** University of California, San Diego  
Contact: Clifford Grobstein, Ph.D., Dean, University of California, San Diego, School of Medicine, La Jolla 92038. (714) 453-2000.
- UCSF:** University of California, San Francisco  
Contact: Seymour M. Farber, M.D., Dean, Educational Services and Director, Continuing Education, Health Sciences, University of California Medical Center, San Francisco 94122. (415) 666-1692.
- USC:** University of Southern California  
Contact: Phil R. Manning, M.D., Associate Dean, Postgraduate Division, University of Southern California School of Medicine, 2025 Zonal Avenue, Los Angeles 90083. (213) 225-1511, ext. 203.

- March 2-20—**Coronary Care for Physicians Training Program.** CRMP Area IV and Cedars-Sinai Medical Center at Cedars of Lebanon Hospital, Los Angeles. Three week course repeated six times through November, designed for practicing internists or cardiologists who will subsequently be working in or directing CCU in community hospitals. Electrocardiography, physical diagnosis, CCU planning and administration, electrolytes and acid-base metabolism, emphasis on practical techniques. Contact: Herbert Stein, M.D., Coronary Care for Physicians Training Programs, Dept. of Cardiology, Cedars of Lebanon Hospital, Box 54265, Los Angeles 90029. (213) 662-9111, Ext. 306.
- March 3-14—**Coronary Care Unit Program for Physicians.** CRMP Area V at Los Angeles County-USC Medical Center. Two week course repeated monthly through May, 1970. Arrhythmia detection, diagnosis and therapy, defibrillation and cardioversion, central venous pressure monitors, placement of pacing catheters, new aspects in diagnosis and treatment of congestive heart failure, shock and associated respiratory problems, and CCU management in community hospitals. Contact: Gladys Ancrum, Dr. P. H., Administrative Associate, CRMP Area V, 1 West Bay State St., Alhambra 91801. (213) 576-1626.
- March 5-6—**Symposium on Endocrinology.** USC at Century Plaza Hotel, Los Angeles. Thursday-Friday. Modern endocrine testing, reproductive endocrinology, general endocrinology. \$65. 14 hrs.
- March 5-6—**Dialogues in Dermatology.** UCSF at Sir Francis Drake Hotel, San Francisco. Thursday-Friday. Veterinary dermatology; atopic dermatitis. The Perineum; vulvar dermatology; genito-urinary dermatology; proctologic dermatology; stomatology and the dermatologist; oto-dermatology; blepharitis; current advances in burn therapy; podiatric dermatology; stasis dermatitis and ankle ulcers; research dermatology. \$65. 14 hrs.
- March 7—**Pediatric Hematology.** UCSF at Childrens Hospital and Adult Medical Center, San Francisco. Saturday. Iron Deficiency, Disorders of Red Cell Enzymes, Erythroblastosis Fetalis, Abnormal Hemoglobin, Blood Smear, Disseminated Intravascular Coagulation, Acute Leukemia, Platelet Disorders, Hemophilia. \$30. 5½ hrs.
- March 14—**Auscultation of the Heart.** PMC. Saturday. Discussion and teaching on the heart sound simulator. 8 hrs.
- March 26—**Obesity.** USC at Hilton Hotel, Los Angeles. Thursday. 6 hrs.
- April 3-4—**Cardiac Arrhythmias in Clinical Practice.** Sacramento-Yolo-Sierra Heart Association at Sacramento Inn, Sacramento. Friday-Saturday. Relevant anatomy and physiology, pharmacology, clinical recognition and treatment of rhythm disturbances of the heart. \$15. Contact: Harold M. Lowe, M.D., Chairman, Symposium Committee, Sacramento-Yolo-Sierra Heart Assoc., Dept. of Cardiovascular-Pulmonary Diseases, Mercy Hospital, 4001 J Street, Sacramento 95819. (916) 456-7881.
- April 3-5—**Sixth Annual Symposium—San Diego Society of Internal Medicine.** Warner Springs Resort, San Diego County. Friday-Sunday. Pulmonary Disease. \$15. Contact: Thomas J. Lehar, M.D., Program Chairman, 6th Annual Symposium, 2001 Fourth Avenue, San Diego 92101. (714) 234-6261.
- April 6-15—**Cardiology for the Consultant—A Clinician's Retreat.** American College of Cardiology at Rancho Santa Fe Inn, Rancho Santa Fe. Ten day program for well-trained clinicians to sharpen ability in the field of cardiology. Contact: William D. Nelligan, Exec. Dir., ACC, 9650 Rockville Pike, Bethesda, Md. 20014. (301) 530-1600.
- April 8—**18th Annual Physicians Cardiovascular Symposium.** Central Valley Heart Association at Fresno Travel Host, Fresno. Wednesday. Premature Coronary Atherosclerosis. Angina Pectoris, Arrhythmias Accompanying Acute Myocardial Infarction, Hyperlemic Patient, Cardiac Auscultation in Pregnancy, Effect of Pharmacological Agents and Postural Changes on Heart Murmurs, Valvular Heart Disease Surgery, Digitalis Glycosides. 7 hrs. Contact: Frances Cuthbertson, Exec. Dir., CVHA, 1759 Fulton Street, Fresno 93721. (209) 237-0288.
- April 8-9—**Medical Surgical Gastroenterology.** USC at Hilton Hotel, Los Angeles. Wednesday-Thursday. 12 hrs.
- April 10—**Annual Symposium on Heart Disease.** Orange County Heart Association at Disneyland Hotel, Anaheim. Friday. Contact: Liggett McLaws. Program Dir., OCHA, P.O. Box 1704, Santa Ana 92702. (714) 947-3001.
- April 10 — **13th Annual Physicians Symposium on Heart Disease.** Santa Clara County Heart Association at San Jose Hyatt House, San Jose. Friday. \$15. 6 hrs. Contact: William G. Allayaud, Exec. Dir., SCCHA, 1984 The Alameda, San Jose 95126. (408) 248-1517.
- April 11—**Myocardial Infarction.** PMC. Saturday. Principles and techniques in a coronary care unit, electrocardiographic diagnosis, therapeutic approach to arrhythmias, heart failure in myocardial infarction, cardiac rehabilitation and the value of exercise, anticoagulation. \$35. 8 hrs.
- April 11-12—**Clinical EMC.** UCSF. Saturday-Sunday.
- April 22-25—**Advances in Endocrinology and Metabolism.** UCSF. Wednesday-Saturday. Intensive review of interrelationships between metabolic disease and endocrine dysfunction, critical evaluation of new developments.
- May 4-22—**Coronary Care for Physicians Training Program.** CRMP Area IV. See March 2-20.
- May 9—**Diseases of the Gastrointestinal Tract.** South Bay Pathology Society and South Bay Radiology Society at Carmel Theater, Carmel. Saturday. Of interest to radiologists, pathologists, and enterologists. \$15. 4 hrs. Contact: Robert Rinehart, M.D., Santa Clara Valley Medical Center, 751 South Bascom Ave., San Jose 95128. (408) 293-0262, Ext 491.
- May 12—**Analytical Approach to Cardiac Diagnosis.** American College of Cardiology and LLU at LLU. Tuesday. Representative cases of heart disease: history, examination, laboratory and radiological procedures. 7 hrs. Contact: William D. Nelligan, Exec. Dir., ACC, 9650 Rockville Pike, Bethesda, Md. 20014. (301) 530-1600.
- May 14-15—**Diagnosis and Clinical Management of Ocular Infections.** UCLA. Thursday-Friday.
- May 15—**California Heart Association—Annual Meeting Scientific Sessions.** Hotel del Coronado, Coro-



nado. Friday. \$10. 7 hrs. Contact: Rodman D. Starke, M.D., 1370 Mission Street, San Francisco 94103. (415) 626-0123.

**May 15-17—Basic Principles of Cardiac Therapy.** PMC and the American College of Cardiology at Jack Tar Hotel, San Francisco. Friday-Sunday. Clarification of pathophysiological basis of various disease states, rational approach to drug usage. \$80 members, \$120 non-members. 24 hrs. Contact: PMC.

**Continuously—Basic Home Course in Electrocardiography.** One year postgraduate series, ECG interpretation by mail. Physicians may register at any time. \$100 (\$2 issues). Contact: USC.

**Continuously—Training in the Procedure of Tonometry.** Northern California Society for the Prevention of Blindness at the Glaucoma Screening Clinic, San Francisco. Weekly Saturday morning program in tonometry for internists and general practitioners. Advance appointment required, no charge. 3 hrs. Contact: Frederic S. Weisenheimer, Ed.D., Executive Director, NCSBP, 4200 California Street, San Francisco 94118. (415) 387-0934.

### **Grand Rounds—Medicine**

#### **Tuesdays**

8:30-10:00 a.m., Assembly Hall, Harbor General Hospital, Torrance. UCLA.

#### **Wednesdays**

10:30-12:00 noon. Auditorium, Medical Sciences Building. UCSF.

11:00 a.m., Room 1645, Los Angeles County-USC Medical Center. USC.

12:30 p.m., Auditorium, School of Nursing, Orange County Medical Center. UCI.

12:30-1:30 p.m., University Hospital, UCSD.

#### **Thursdays**

10:30-12:00 noon, Room 33-105, UCLA Medical Center. UCLA.

#### **Fridays**

8:00 a.m., Courtroom, Third Floor, Kern County General Hospital, Bakersfield. CRMP Area IV.

8:30 a.m., Auditorium, Lebanon Hall, Cedars of Lebanon Hospital, Los Angeles. CRMP Area IV.

Infectious Disease Grand Rounds. 10:00 a.m., Auditorium, Childrens Division Building, Los Angeles County-USC Medical Center, Los Angeles. USC.

Neurology. 10:15 a.m., held alternately at Stanford University Hospital and Neurology Conference Building 7, V.A. Hospital, Palo Alto. STAN.

1st and 3rd Fridays, 11:00 a.m., Auditorium, Brown Building, Mount Sinai Hospital, Los Angeles. CRMP Area IV.

1:15 p.m., Lieb Amphitheater, Timken-Sturgis Research Bldg., La Jolla. Scripps Clinic and Research Foundation.

Rheumatology Grand Rounds. 11:45 a.m., Room 6441, Los Angeles County-USC Medical Center, Los Angeles. USC.

### **OBSTETRICS AND GYNECOLOGY**

**February 20-21—Birth Prevention: The Growing Challenge to Physicians and to the Community.** UCSF.

Friday-Saturday. Birth prevention, contraception, role of contraceptive clinic, unmarried teenager, sex education in schools, use and complications of IUD and Pill, patient attitudes, future methods, therapeutic abortion, physician attitudes toward therapeutic and elective abortion, techniques of therapeutic abortion, female sterilization. \$60. 11½ hrs.

**May 15-16—Obstetrics and Gynecology Symposium.** Southern California Permanente Medical Group and Kaiser Foundation Hospitals at Beverly Hilton Hotel, Beverly Hills. Friday-Saturday. Contact: Shirley Gach, Rm. 6014, So. Calif. Permanente Med. Group, 4900 Sunset Blvd., Los Angeles 90027. (213) 663-8411.

### **Grand Rounds—Obstetrics and Gynecology**

#### **Mondays**

10-11:30 a.m., Assembly Room, First Floor, Harbor General Hospital, Torrance. UCLA.

#### **Fridays**

8 a.m., Auditorium, Orange County Medical Center. UCI.

### **PEDIATRICS**

**March 7—Pediatric Hematology.** UCSF. See Medicine, March 7.

**March 12-14—Pediatric Neurology.** UCSF. Thursday-Saturday. Review of neurological examinations and procedures, paroxysmal neurological disorders, metabolic problems in pediatric neurology, disorders of movement. \$75.

**March 13-14—Fourth Annual Pediatric Spring Clinic—Sacramento County Pediatric Society.** Sacramento Inn, Sacramento. Friday-Saturday. Contact: Vernon L. Walton, M.D., Secretary, SCPS, 3811 Florin Road, Sacramento 95823. (916) 422-6635.

**March 20-21—Pulmonary Disease in Newborns.** UCI, CRMP Area VIII in cooperation with the National Cystic Fibrosis Research Foundation at Childrens Hospital of Orange County. Friday-Saturday. Registration by March 1 is necessary. Contact: Bruce D. Ackerman, M.D., Dept. of Pediatrics, UCI.

**April 3-4—Pediatric Symposium—Nephrology.** Southern California Permanente Medical Group and Kaiser Foundation Hospitals at Ambassador Hotel, Los Angeles. Friday-Saturday. Contact: Shirley Gach, Rm. 6014, So. Calif. Permanente Med. Group, 4900 Sunset Blvd., Los Angeles 90027. (213) 663-8411.

**April 4-5—Armchair Allergy.** PMC at International Inn, San Francisco. Saturday-Sunday. Early diagnosis, role of steroids in management of asthma, skin tests, current concept of the basic steps in the allergic reaction. \$50. 14 hrs.

**April 17-18—Infectious Diseases.** UCSF at Childrens Hospital, San Francisco. Friday-Saturday. For pediatricians, family physicians, internists and clinically oriented bacteriologists.

**April 22-25—The Hospitalized Child, His Family and His Community.** American Association for Child Care in the Hospital, Stanford Children's Convalescent Hospital, UCSF and STAN at Sheraton-Palace Hotel, San Francisco. Wednesday-Saturday. 15 hrs. Contact: Helen H. Glaser, M.D., Stanford Children's Convalescent Hospital, 520 Willow Road, Palo Alto 94304. (415) 327-4800.



May 7-9—**Advances in Pediatrics.** UCSF. Thursday-Saturday. Review of major reappraisals in some aspects of the specialty, clinical implications of advances in cytology, physiology, immunology and endocrinology.

## Grand Rounds—Pediatrics

### Tuesdays

8:30 a.m., Auditorium, Childrens Division Building, Los Angeles County-USC Medical Center, Los Angeles. USC.

8:30 a.m., Room 4-A, Kern County General Hospital, Bakersfield. CRMP Area IV.

8:30 a.m., Pathology Auditorium, San Francisco General Hospital.

### Wednesdays

8-9:00 a.m., held alternately at Auditorium, Orange County Medical Center and Auditorium, Childrens Hospital of Orange County. UCI.

8:30 a.m., Bothin Auditorium, Childrens Hospital, San Francisco.

### Thursdays

8:30-10:00 a.m., Room 664, Science Building, UCSF.

8:30-9:30 a.m., Lebanon Hall, Cedars of Lebanon Hospital, Los Angeles.

8:30 a.m., First Floor Auditorium, Harbor General Hospital, Torrance.

### Fridays

8:00 a.m., Lecture Room, A Floor, Health Sciences Center, UCLA. CRMP Area IV.

8:30 a.m., Stanford University Medical Center, Palo Alto.

8-9:00 a.m., Lecture Hall, Childrens Hospital of Los Angeles.

## PSYCHIATRY

February 26-April 30—**Teaching Clinics in Psychiatry.** UCLA. Thursdays. 20 hrs.

March 14-15—**Modern Theories in Psychiatry.** UCSF at Napa State Hospital, Imola. Saturday-Sunday. 5 hrs.

March 14-15—**The Troubled Adolescent in the Modern Family.** UCSF. See Adolescent Medicine, March 14-15.

March 20-21 — **Suicide Prevention—Advanced Workshop.** UCSF. Friday-Saturday.

March 21—**Psychiatric Perspectives in Medicine—An Introduction to Family Evaluation and Family Intervention.** UCSF at Stockton State Hospital, Stockton. Saturday. Principles of family organization, methods of family assessment, demonstration of family interview. 4½ hrs. \$7.50.

March 23-26—**The Urban Scene.** American Orthopsychiatric Association. See Community Medicine, March 23-26.

April 4-5—**The Brain and Its Behavior.** UCSF at Agnews State Hospital, San Jose. Saturday-Sunday. New developments in chemistry, neuroanatomy, and neurophysiology related to human behavior. \$15. 11 hrs.

April 8-June 10—**Group Methods.** UCSF at V.A. Hospital, San Francisco. Wednesdays 11:30-1:00. Weekly lectures and participants assigned to clinic groups. \$25. 15 hrs.

April 18-19—**New Approaches to the Care of the Suicidal Patient.** UCLA. Saturday-Sunday.

May 2-3—**Further Explorations in Group Therapy.** UCSF at Modesto State Hospital, Modesto. Saturday-Sunday.

May 8-10—**American Academy of Psychoanalysis—Annual Meeting.** Jack Tar Hotel, San Francisco. Friday-Sunday. Contact: Mollie Carroll, 125 East 65th Street, New York 10021. (212) 879-8950.

May 8-10—**Society for Biological Psychiatry.** Hilton Hotel, San Francisco. Friday-Sunday. Contact: George N. Thompson, M.D., Sec.-Treas., SBP, 2010 Wilshire Blvd., Los Angeles 90017. (213) 483-7863.

May 8-11 — **American Psychoanalytic Association.** Sheraton Palace Hotel, San Francisco. Friday-Monday. Contact: Mrs. Helen Fischer, Exec. Sec., APA, 1 East 57th Street, New York 10022. (212) 265-0430.

May 9-10—**Psychiatry and the Law.** UCSF at Humboldt State College, Arcata. Saturday-Sunday.

May 10—**Association for the Advancement of Psychotherapy.** Civic Auditorium, San Francisco. Sunday. Contact: Stanley Lesse, M.D., Pres., AAP, 15 W. 81st Street, New York 10024. (212) 873-9233.

May 11-15—**American Psychiatric Association.** Civic Auditorium and Brooks Hall, San Francisco. Monday-Friday. Contact: Robert S. Garber, M.D., Executive Sec., Carrier Clinic, Belle Mead, New Jersey 08502. (201) 359-3101.

May 14-16—**2½ Day Symposium on Mental Health.** UCSF. Thursday-Saturday.

## RADIOLOGY—PATHOLOGY

March 1-6—**American Radium Society.** Hotel del Coronado, Coronado. Sunday-Friday. Uses of radiation and results in treatment of cancer and allied conditions. Contact: John V. Blady, M.D., Secretary, ARS, 2201 Benjamin Franklin Parkway, Philadelphia 19130. (215) 564-4741.

March 3-7—**Diagnostic Radiology.** UCSF. Tuesday-Saturday. Primarily for practicing radiologists. \$30/day, \$125/5 days. 27 hrs.

March 9—**Granulomatous Colitis in Association with Diverticula.** UCSF Department of Radiology and the San Francisco Radiological Society. Monday 8 p.m. 1 hr. Contact: M. B. Ozonoff, M.D., Assistant Prof. of Radiology, UCSF. (415) 648-8200, ext. 414.

April 1-5—**Clinical Cytology for Pathologists.** UCSF at St. Francis Hotel, San Francisco. Wednesday-Sunday. Cytopathology of urinary tract, female genital tract following irradiation, non-neoplastic lesions of the lung.

April 17-30—**Radiology of the Gastrointestinal Tract.** USC, Princess Carla Cruise to Mexico from Los Angeles. Two weeks. \$200. 28 hrs.

Continuously—**Principles and Clinical Uses of Radioisotopes.** UCSF. Fundamentals for the proper understanding and use of radioactivity in clinical medicine. Training in diagnostic and therapeutic uses of radioisotopes. Normal period of training: 3 months. Two part course: Part A, Basic Fundamentals; Part B, Clinical Applications.

Continuously — **Mammography.** UCSF Mammography Section, Department of Radiology. Three days weekly, beginning with Tuesday. Call several days in advance. Contact: Richard H. Gold, M.D., Mammography Section, Department of Radiology, UCSF. (415) 666-1918.

#### **Grand Rounds—Radiology**

##### **Fridays**

Neuroradiology Grand Rounds. 9:30 a.m., held alternately at Stanford University Hospital and Neurology Conference Building 7, V.A. Hospital, Palo Alto, STAN.

#### **SURGERY—ANESTHESIOLOGY**

February 25-March 1—**Controversial Areas in Surgery.** UCLA at El Mirador Hotel, Palm Springs. Wednesday-Saturday. Upper intestinal bleeding, treatment of bleeding esophageal varices, pancreatic-duodenectomy, breast cancer surgery, Hirschsprung's Disease, toxic megacolon and fulminant colitis, lower gastrointestinal bleeding, pulmonary embolism, organ transplantation, automated multiphasic laboratory screening, recurrent intestinal obstruction, cancer of the rectum, cancer of the thyroid. \$125. 16 hrs.

February 28-March 1 — **The Physician and Athletics.** UCSF. Friday-Saturday. 13½ hrs.

March 13-14—**Surgical Symposium — Changing Concepts in Surgery.** Southern California Permanente Medical Group and Kaiser Foundation Hospitals at Newporter Inn, Newport Beach. Friday-Saturday. Contact: Shirley Gach, Rm. 6014, So. Calif. Permanente Med. Group, 4900 Sunset Blvd., Los Angeles 90027. (213) 663-8411.

March 14-15—**Techniques of Surgery of the Foot.** UCLA. Saturday-Sunday.

March 25-28—**Neurosurgical Society of America.** Ojai Valley Inn, Ojai, Calif. Wednesday-Saturday. Contact: William F. Collins, M.D., Secretary, NSA, 789 Howard Avenue, New Haven, Conn. 06510. (203) 436-1212.

April 8-9 — **Medical Surgical Gastroenterology.** See Medicine, April 8-9.

April 9-10—**General Surgery.** UCSF at St. Francis Hotel, San Francisco. Thursday-Friday. \$65. 11½ hrs.

April 11-12—**Los Angeles County Society of Anesthesiologists—15th Annual Postgraduate Assembly.** Los Angeles Hilton Hotel. Saturday-Sunday. Contact: Leo A. Parker, M.D., 8422 Jamieson Street, Northridge 91324. (213) 345-6763.

#### **Grand Rounds—Surgery**

##### **Wednesdays**

7:15 a.m., Auditorium, Kern County General Hospital, Bakersfield. CRMP Area IV.

1st and 3rd Wednesdays. 11:00 a.m., Auditorium,

Brown Building, Mount Sinai Hospital, Los Angeles. CRMP Area IV.

##### **Thursdays**

Neurology and Neurosurgery Grand Rounds. 11:00-12:15. Room 663, Science Building, UCSF.

##### **Fridays**

12:00 p.m., Auditorium, Orange County Medical Center, Orange. UCI.

Neurosurgery. 11:15 a.m., held alternately at Stanford University Hospital and Neurology Conference Building 7, V.A. Hospital, Palo Alto, STAN.

##### **Saturdays**

8:00 a.m., Auditorium, 1st floor, University Hospital of San Diego County, San Diego. UCSD.

9:00 a.m., Room 73-105, Health Sciences Center, UCLA. CRMP Area IV.

8:30 a.m., Assembly Room, Harbor General Hospital, Torrance. CRMP Area IV.

#### **OF INTEREST TO ALL PHYSICIANS**

##### **CMA Postgraduate Institutes and Circuit Courses**

April 2-3—**West Coast Counties Regional Postgraduate Institute.** CMA, UCD and Monterey County Medical Society at Del Monte Hyatt House, Monterey. Thursday-Friday. Endocrine Problems with Children (including Diabetes), Infectious Diseases, Cardiac Disease and its Rehabilitation, the Physician and Family Problems. \$20. 11 hrs. Contact: CMA.

May 8-9—**San Joaquin Valley Counties Regional Postgraduate Institute.** CMA, USC, and Fresno County Medical Society at Ahwahnee Hotel, Yosemite. Friday-Saturday. Concurrent symposia in Adolescent Medicine, Coronary Care, Sensitivity Training, and Problems in the Practice of Medicine. \$20. Contact: CMA.

May 15-16 — **Redwood Regional Conference.** CMA, UCSF at Konoti Harbor Inn, Clear Lake. Friday-Saturday. The Anemias and Musculo/Skeletal Conditions in Daily Practice. \$20.

February 15—**Hollywood Community Hospital Annual Symposium.** Sheraton-Universal Hotel, Hollywood. Sunday. Contraceptive and Sexual Problems. Contact: Viola Kindstrand, Symposium Secretary, Hollywood Community Hospital, 6245 de Longpre Ave., Hollywood 90028. (213) 462-2271.

February 15-19—**Loma Linda University School of Medicine, Alumni Association—Postgraduate Convention.** Ambassador Hotel, Los Angeles, and LLU. Sunday-Thursday. Sunday-Monday: Refresher course, LLU. Tuesday-Thursday: Scientific Assembly, Ambassador Hotel. 32 hrs. Contact: Alma O. Johnson, Managing Director, Alumni Postgraduate Convention for 1970, 1832 Michigan Avenue, Los Angeles 90033. (213) 262-2173.

February 26-April 30—**Teaching Clinics in Psychiatry.** See Psychiatry, February 26-April 30.

February 28—**Problems in Social Change Reflected in Medical Practice.** UCSF. See Community Medicine, February 28.

March 7-11—**California Medical Association—Annual Scientific Assembly.** Hilton Hotel, San Francisco. Saturday-Wednesday. General Sessions: Saturday p.m.: Family Practice. Sunday p.m.: Manpower. Monday p.m.: Systems of Delivery of Medical Care. Tuesday p.m.: Birth Defects. Guest Speakers for General Sessions include: Lynn P. Carmichael, M.D., University of Miami School of Medicine; Mike Gorman, National Committee Against Mental Illness; Jerome Pollack, Associate Dean for Medical Care Planning, Harvard Medical School; Henry K. Silver, M.D., Professor of Pediatrics, University of Colorado Medical Center; Eugene A. Stead, Jr., M.D., Duke University Medical Center. Assembly includes special conferences, section meetings, and medical motion picture symposia daily.

March 19-20 — **Postgraduate Seminar and Clifford Sweet Memorial Lecture.** Childrens Hospital of Oakland. Thursday-Friday. Sex Education for Physicians. Contact: Inetta Carty, Childrens Hospital of Oakland, 51st and Grove Streets, Oakland 94609. (415) 654-5600.

March 25-26 — **Los Angeles County Heart Association and Los Angeles Academy of General Practice—Seventh Annual Spring Symposium for Physicians Practicing General Medicine.** Wednesday-Thursday. Contact: Joe Kennelly, Director, Public Information, LACHA, 2405 W. Eighth Street, Los Angeles 90057. (213) 385-4231.

April 17-18—**Infectious Diseases.** UCSF. See Pediatrics, April 17-18.

April 19—**Office Emergencies: A Symposium for Medical Assistants.** UCSF. Sunday.

April 25-26—**Comparative Medicine.** UCSF. Saturday-Sunday. Professionals in the fields of veterinary medicine, pediatrics, public health and microbiology.

April 25-26—**Sex in Modern Society.** UCSF at Flamingo Motor Hotel, Santa Rosa. Saturday-Sunday. \$15. 8 hrs.

May 1-2—**Trauma.** UCSF at Mary's Help Hospital, Daly City. Friday-Saturday.

May 3-9—**Hawaii Medical Association.** Hawaiian Village, Honolulu. Sunday-Saturday. Contact: Miss Lee McCaslin, Exec. Sec., HMA, 510 Beretania Street, Honolulu 96813. (808) 536-7702.

Continuously—**Audio-Digest Foundation.** A non-profit subsidiary of CMA. Twice-a-month tape recorded summaries of leading national meetings and surveys of current literature. Services by subscription in: General Practice, Surgery, Internal Medicine, Ob/Gyn, Pediatrics, Anesthesiology, Ophthalmology. Catalog of lectures and panel discussions in all areas of medical practice also available. Contact: Mr. Claron L. Oakley, Editor, 619 S. Westlake Ave., Los Angeles 90057.

## TELEVISION

**Southern California's Medical Television Network.** UCLA. Weekly broadcasts, Tuesdays 8:30 a.m. Contact: UCLA Medical Television. (213) 825-1341.

February 17—**Venereal Disease.** UCLA School of Medicine.

February 24—**Allergy Report.** University of Western Ontario, Canada.

March 3—**Fits.** British Broadcasting Corporation.

March 10—**Valvular Heart Disease, Part I.** Washington-Alaska Regional Medical Programs.

March 17—**Valvular Heart Disease, Part II.** Washington-Alaska Regional Medical Programs.

March 24—**Valvular Heart Disease, Part III.** Washington-Alaska Regional Medical Programs.

March 31 — **Inhalation Therapy and IPPB.** Medical Television Network.

**Santa Clara County Medical Society's MD-TV.** Weekly broadcasts, Thursdays 7:30 p.m. Channel 54, Greater San Jose Area. Of educational value to both physicians and nurses. Contact: Roger Brown, Santa Clara County Medical Society, 700 Empey Way, San Jose 95128 (408) 286-5050.



# BOOK REVIEWS

**MENIERE'S DISEASE**—A Symposium Reprinted from The Otolaryngologic Clinics of North America, October 1968—Edited by Jack L. Pulec, M.D., The Mayo Clinic and Mayo Foundation, Rochester, Minn. W. B. Saunders Company, West Washington Square, Philadelphia, Pa. (19105), 1968. 715 pages, \$15.00.

In anticipating the reading of *Meniere's Disease* edited by Jack L. Pulec, M.D. of the Mayo Clinic one should give consideration to the fact that this is a reprinting of the symposium of the experts nationally and internationally in otology and particularly otological surgery and that they, themselves, are wrestling with the difficult problem of separating it from the other myriad similar conditions, of classifying it and in short, trying to basically organize it along scientific lines. Perhaps one would get some idea of the slant of the book in noticing that the single chapter on the medical treatment of Meniere's disease written by Eugene L. Derlacki of Northwestern University totals some 12 pages of which seven are taken up with graphs and the presentation of five case histories. The obvious emphasis on surgical approaches to this disease should not be taken as indication that surgery is now the method of choice for treatment of this condition. For one who is looking for in-depth reporting in certain isolated areas of the basic sciences related to Meniere's disease and labyrinth function in general, this book can be an interesting acquisition.

BERNARD M. KRAMER, M.D.

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**CLINICAL ASPECTS OF OPERABLE HEART DISEASE**—Donald R. Kahn, M.D., Associate Professor of Surgery, University of Michigan Medical School; Ruth H. Strang, M.D., Associate Professor of Pediatrics and Communicable Disease, University of Michigan Medical School and Director of Pediatrics, Wayne County General Hospital; and William S. Wilson, M.D., Professor of Medicine and Chief of Cardiology, Rutgers Medical School. Appleton-Century-Crofts, Division of Meredith Corporation, 440 Park Avenue South, New York, N. Y. (10016), 1968. 363 pages, \$16.00.

This comprehensive review of what has become a large field attempts to encompass every aspect of cardiac surgery in its compact 360 pages. In reviewing extracorporeal circulation, diagnostic cardiology, differential diagnosis, surgical technique, histopathology, pathophysiology and management, the authors have necessarily provided a series of condensations in which several important omissions are evident to the reviewer. The lack of concentration on any of these important aspects makes it difficult to ascertain the intended purpose of the book. As a review for medical students it is too extensive; as a reference it is incomplete; and as a guide for aspiring cardiac surgeons it is too superficial. The language of its text varies from the sophisticated jargon of the cardiac surgeon to elementary description suitable for lay readers.

Abundant illustrations include some excellent photographs and diagrams, but the drawings of surgical techniques are poor and inaccurate (one shows an aortic valve prosthesis implanted upside down).

In light of the importance of clinical experience in this rapidly advancing field, the book is conspicuous in its ab-

sence of at least contributing authorship by the renowned senior cardiac surgeon whose teaching it reflects.

BENSON B. ROE, M.D.

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**THE APOLOGIE AND TREATISE OF AMBROISE PARE**—Containing the Voyages Made Into Divers Places—Edited and with an introduction by Geoffrey Keynes, M.D., F.R.C.S., F.R.C.O.G. Dover Publications, 180 Varick Street, New York, N.Y. (10014), 1968. 227 pages, \$2.50.

From the time of Alessandro Benedetti in the fifteenth century to Harvey Cushing in the twentieth, surgeons following in the trains of armies have given us in their journals vivid impressions from the field. One of the most important and fascinating of these journals is that of the great French surgeon Ambroise Paré. Paré saw and commented upon some of the most significant events in the history of France during the sixteenth century in his *Apologie and Treatise*, here reproduced from the edition edited by Geoffrey Keynes in 1952, and to which is added a selection of the surgical writings of the father of modern surgery.

The version reproduced both of the *Apologie* and of the selected writings is from Thomas Johnson's translation of Paré's *Workes*, issued in 1634. Unfortunately this translation, although nearly contemporary, is not very good, containing many omissions, transpositions, and other distortions due in part to having been made from a poor Latin translation of the French original. Readers should be warned that dates are misquoted, technical terms frequently misunderstood, and the sense often rendered imperfectly. Nonetheless, the rendering possesses much of the color and flavor of the times. However, there are other more accurate versions, especially of Paré's journeys, such as those of Steven Paget and Francis Packard. With this *caveat*, this inexpensive reproduction will be a welcome addition to the young surgeon's library and will delight him.

J. B. DEC. M. SAUNDERS, M.D.

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**DIAGNOSIS OF SURGICAL DISEASE**—Volumes I, II, and III—Richard T. Shackelford, M.D., Associate Professor of Surgery, The Johns Hopkins University School of Medicine. W. B. Saunders Company, West Washington Square, Philadelphia, Pa. (19105), 1968. 2131 pages, total in volumes I, II, and III; \$72.50.

*Diagnosis of Surgical Disease* is a three-volume work, edited and written by Richard Shackelford with the assistance of 23 contributors. It provides an extraordinarily comprehensive and detailed account of every phase of surgical diagnosis, including Cytopathology, Radioisotope Scanning, Skin Disorders of Surgical Interest, Special Fungus Infections, and chapters on all of the surgical specialties. Beautifully produced, and in general well written, it is a splendid contribution to the field of surgical diagnosis.

Volume I contains "The History: Significant Symptoms," "The Physical Examination," "Cytopathology . . ."

"Radioisotope Scanning . . .," and a series of chapters on such diverse subjects as "Tumors of the Head and Neck," "Heart Disease in Children," and "Lesions of the Esophagus." Volume II, written almost entirely by Dr. Shackelford, covers the lesions of the gastrointestinal tract. This is the best written and most readable of the three volumes. The third volume covers "Peripheral Vascular Disease," "Skin Disorders . . .," Urology, Gynecology, Orthopedics, Lesions of the Hand, Surgical Endocrinology, Fungus Infections, "Postoperative Complications," and "Surgical Diagnosis in the Newborn."

Except for major portions of Volume II, even the beginner will find this too massive a work to read through. It is designed primarily for special consultation and supplementary reading. It is somewhat repetitious and disjointed in that under the routine physical examination the breast is omitted, and is included in great detail in a special chapter on the breast. The rectal and pelvic examinations are also omitted from the chapter on the routine physical examination. The chapter on radioisotope scanning is interesting and informative, but the reviewer questions its appropriateness in a three-volume work on surgical diagnosis, in view of the rapid advances being made in this field. Indeed, the author predicts that there will be very rapid and substantial changes in the near future.

Despite these criticisms, this is a monumental contribution for which the editor and principal author should be congratulated. It will undoubtedly adorn the "Do Not Take From Library" desk of many institutions for some years to come, and will be consulted with profit by students of surgery at all stages of their careers.

J. ENGLEBERT DUNPHY, M.D.

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**DIAGNOSIS AND MANAGEMENT OF PAIN SYNDROMES—Second Edition**—Bernard E. Finneson, Chief of Neurological Surgery, Crozer-Chester Medical Center, Chester, Sacred Heart Hospital, Chester, Taylor Hospital, Ridley Park, Pennsylvania. W. B. Saunders Company, West Washington Square, Philadelphia, Pa. (19105), March 25, 1969. 337 pages, \$12.50.

The author presents a good review of the diagnosis and management of pain syndromes. This is approached systematically by anatomical regions such as neck, low back, face, headache, visceral, vascular and so forth. Discussions are succinct with pertinent points on diagnosis, also treatment both conservative and surgical. The presentation of specific entities or problems is of necessity somewhat abbreviated and in some instances may require additional reading or reference work.

This second edition is enhanced with the addition of two sections, one on the use of drugs in relief of pain with advantages and undesirable side-effects of various drugs, by Arthur Grollman, M.D., Ph.D.; and a second section on the management of musculoskeletal pain, by Martin Meltzer, M.D.

Illustrations are line drawings and in general are very satisfactory, showing regional anatomical features, also well outlined dermatome patterns and some basic or pertinent steps in surgical procedures.

In the treatment of low back pain, two exercises, namely, numbers 4 and 5 (Fig. 9-16) are questionable and may tend to aggravate rather than help. Also in the illustration (Fig. 9-19) the Knight back brace holds the patient in a sway back or an increased lumbar lordosis, and which tends in fact to contradict the illustration (Fig. 9-15) showing proper and improper posture.

The book is recommended, is easy to read, and covers basic principles in dealing with pain syndromes.

PAUL E. McMASTER, M.D.

**MOTOR NEURON DISEASES—Research on Amyotrophic Lateral Sclerosis and Related Disorders—Contemporary Neurology Symposia, Volume II**—Edited by Leonard T. Kurland, Rochester, Minnesota; and Forbes H. Norris, Jr., San Francisco. Grune & Stratton, Inc., 381 Park Avenue South, New York, N.Y. (10016), 1969. 407 pages, \$13.25.

This volume, based on a symposium held in San Francisco in 1967, continues the high standard set by Volume I of the series, which dealt with non-metastatic effects of cancer on the nervous system. I know of no other book, old or new, where the reader interested in motor neuron diseases can find a comparable breadth of useful information.

Although amyotrophic lateral sclerosis (ALS) may seem a discouraging disease to study, in the past decade there has been a profusion of new work on this and related diseases. A whole class of previously unrecognized hereditary motor neuron diseases has been delineated, and great interest has centered on the endemic ALS which accounts for 10 percent of adult deaths in Guam. The present volume conveys some of the excitement generated by the incursion of new knowledge in a formerly static subject.

The papers include useful data on the history, geographical distribution and course of ALS and of the genetically determined infantile, juvenile and adult types of progressive muscular atrophy. Gaumanian ALS receives much attention, although the hope that it would shed light on the cause of ordinary ALS is not yet realized. Elegant summaries of the pathology and electromyographic features of ALS are provided, and a large amount of laboratory research on etiology, pathogenesis and therapy is summarized. Particularly exciting is Gibbs and Gajdusek's account of the successful transmission of kuru and Creutzfeldt-Jakob disease to non-human primates. Lower motor neuron degeneration is a feature of the latter disease, a fact which justifies cautious optimism in the continuing search for an infectious cause of ALS.

This book is well-edited and printed, with photomicrographs of high quality. It is an excellent source of information on a major category of neurological disease.

ROBERT B. LAYZER, M.D.

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**INTERNAL MEDICINE IN WORLD WAR II—Volume III, Infectious Diseases and General Medicine (Medical Department, United States Army)**. Prepared and published under the direction of Lt. Gen. Leonard D. Heaton, the Surgeon General, United States Army. Col. Robert S. Anderson, MC, USA, Editor in Chief, and W. Paul Havens, Jr., M.D., Editor for Internal Medicine. Office of the Surgeon General, Department of the Army, Washington, D.C., 1968. For sale by the Superintendent of Documents, U.S. Government Printing Office, Washington, D.C., 20402, \$8.25. 778 pages (Buckram).

The editor describes this volume as "a potpourri"—"concerned with infectious diseases, general medicine and dermatology." This it is, descriptions of a variety of medical conditions in the army during World War II by 24 very distinguished authors.

Coming some 24 years after the war, it is obvious that these accounts are of value chiefly for their historical importance. However, the descriptions of tropical diseases—leishmaniasis, schistosomiasis, the heart in scrub typhus, filariasis, are valuable references still for anyone going to these areas or seeing such diseases.

Of particular interest to Californians is the chapter on coccidioidomycosis written by Roger Egeberg, now Assistant Secretary of HEW. The work of C. E. Smith and many other old Stanford colleagues is given due recognition.

The fact that it took me some 2 months to finish this volume is perhaps the best measure of my over all appraisal—it was interesting, instructive reading—in small doses.

G. B. ROBSON, M.D.





## Health Sciences Construction Bonds

**PROPOSITION 1**—the Health Sciences Construction Bond Issue—is aimed at relieving the shortage of health manpower in California.

If approved by the voters in the June 2, 1970 election, it would provide \$246.3 million to construct and expand training facilities in the health sciences on six of the state's university campuses.

The urgent need now for more health professionals—physicians, dentists, nurses, pharmacists, optometrists, public health experts and veterinarians—has already been stressed in state and national reports. The situation will undoubtedly become more serious in the next few years—the inevitable result of California's soaring population, the growing public awareness of the benefits of high-quality health care, and the continuing expansion of private and governmental health insurance programs.

The basic legislation for Proposition 1 was overwhelmingly approved by the Legislature and was signed by Governor Reagan on September 4, 1969. It requires only a simple majority—not a two-thirds vote—for passage in the June election.

Major provisions of the proposition are these:

- Completion of the three new medical schools: Davis (\$56.3 million), Irvine (\$54.1 million), and San Diego (\$43.2 million).
- Expansion of the medical schools at San Francisco (\$27.4 million) and Los Angeles (\$6.6 million).
- Expansion of the dental schools at San Francisco (\$13.7 million) and Los Angeles (\$1.6 million).
- Expansion of the school of nursing at San Francisco (\$0.3 million), the school of optometry at Berkeley (\$2.0 million), the school of public

health at Berkeley (\$6.9 million), and the school of veterinary medicine at Davis (\$22.2 million).

- Provision of general campus support facilities at the San Francisco Medical Center (\$7.7 million) and provision of initial facilities at the new School of Human Biology at San Francisco (\$2.8 million).


- Feasibility studies and planning for a second school of veterinary medicine, to be located in Southern California (\$200,000).

Implementation of the entire program would result in a 125 percent increase in the number of physicians graduating each year from University of California medical schools, a 28 percent increase in the number of dentists, a 38 percent increase in the number of pharmacists, a 13 percent increase in the number of nurses, and a 62 percent increase in the number of veterinarians.

State officials have emphasized that the bond issue does not represent a blank-check authorization; the State Legislature must thereafter approve and appropriate funds for each specific construction project submitted by the university and approved by the State Director of Finance.

Based on the assumption that the population will reach 28 million during the 1980s, the bond issue will cost the average Californian about 70 cents per year over the 25-year life of the bond issue, or a per capita total of about \$18. If the bonds are amortized over a shorter period, the cost would be substantially less. The funds would come from general revenues, and would not raise property taxes.

If Proposition 1 is approved, the university should attract \$126.7 million in matching construction funds from the Federal Government.







## Editorial

# THE HEALTH BONDS A Mandate for Proposition 1

THE 1969 HOUSE OF DELEGATES resolved "that CMA urge the University of California, the Governor, the Legislature and the people of California to provide financial support for capital construction needs for medical and health science education at the several campuses of the University as soon as possible." This action was taken in recognition of the fact that this was necessary to protect both the health and the pocketbooks of the people of California.

Subsequently and with full support from CMA, a Health Science Construction Bond Proposition was prepared and placed on the June 1970 ballot by an act of the Legislature which was passed unanimously by both the Assembly and the Senate and signed by the Governor. The first necessary steps to carry out the mandate of the House of Delegates have thus been taken. It now remains for the people of California to give *their* mandate to the State and to the University by passing Proposition 1 in the primary election this coming June.

No one who has studied the problem of health manpower in California questions the absolute need for the health science facilities which are to be provided by this bond issue. They do question whether enough voters understand how vitally this issue affects both their health and their pocketbooks. The simple fact is that if Proposition 1 fails of passage at this time the already critical shortages of doctors and other health personnel can only become more critical, and the ultimate cost, when what has to be done inevitably is done, will be immeasurably greater than it is today. The


loss to the people would be both in health care and in money.

Bond issues have fared poorly in recent elections, to put it mildly. It has become a sort of habit of the electorate to vote down bond issues more or less regardless of their merit. Yet there are some things which *must* be had if the quality of life is to be maintained. Health care is one of these things. The \$246,300,000 which the Health Science Bonds can provide will produce educational facilities and increase resources which must be had to protect the level of health care in California. It is quite impractical to do this on a pay-as-you-go basis over the short span of time during which the money will be needed. The amount is too great and besides the benefits will largely accrue in years to come, the years during which these bonds will be amortized.

Somehow the mandate of the House of Delegates must become the mandate of the people of California on June 2, 1970. There is lack of information and apathy to be overcome. Proposition 1 will not pass by itself. A truly aggressive effort is needed to inform the voters and galvanize them to action. It is the privilege and also the duty of a free profession to act vigorously and effectively in the interests of the society it serves. This is one of those times when physicians and all other allied health professionals must roll up their sleeves and go to work to get the Health Bonds passed, and this in the public interest.

We can and must make Proposition 1 the mandate of the people.

(See bond facts on obverse page.)



# Coagulation Factor Analysis in Patients On Long-Term Anticoagulation

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■ *Ninety studies on 58 patients undergoing chronic warfarin therapy included Quick prothrombin times, partial thromboplastin times, thromboplastin generation tests and assays for clotting factors II, V, VII, VIII, IX, X, XI and XII. The results indicate no benefit from supplementation of the Quick tests by any of these other procedures. It is suggested that the Quick test uniformly performed, using a standard uniform thromboplastin, would be the procedure of choice.*

COUMARIN DERIVATIVES for oral administration are the most practical agents for long-term anticoagulation. Careful screening of patients, with emphasis on alcoholism and hypertension and on detecting lesions which may bleed, helps to avoid complications. The attending physician must be aware of other drugs which affect the absorption, binding, and utilization of the anticoagulant as well as the balance with vitamin K.<sup>1</sup> In spite of

all caution there is still a disturbing frequency of bleeding. Purpura, ecchymosis, menorrhagia and epistaxis may occur in 40 to 50 percent of patients but are usually minor. The incidence of serious or life-threatening bleeding varies in reported series. In 2,189 cases collected from the literature,<sup>2</sup> 5.6 percent of patients had serious bleeds, mostly gastrointestinal, urinary and intracerebral.

The correct dose of coumarin anticoagulant is commonly determined by its effect on the prothrombin time as determined by the method of Quick. The Quick prothrombin time is affected by depression of those coagulation factors in-

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fluenced by coumarins (Factors II, VII, and X) as well as by two others (Factor V and fibrinogen). It is not influenced by Factor IX, which is lowered by the anticoagulant. It has been suggested by some authorities that bleeding which occurs in the presence of Quick prothrombin time within the usual therapeutic range may be explained by undetected disproportionate depression of Factor II,<sup>3</sup> Factor X<sup>4</sup> or Factor IX.<sup>5</sup> This naturally leads to the conclusion that alternative or supplementary procedures to the Quick prothrombin time determination are necessary. In contrast to these reports, other publications have indicated that clotting factors depressed by long-term coumarin therapy are affected to a consistent extent, which correlates with the results of the Quick test.<sup>6-8</sup>

Differences in the procedures used to assay coagulation factors could explain the conflicting results. Tissue thromboplastins are known to vary in their relative sensitivity in detecting deficiency of different clotting factors. A further report on the relation between results with the Quick prothrombin time and specific coagulation factor assays thus seems warranted. The data to be presented do not support the notion that disproportionate depression of an individual clotting factor undetected by the Quick test is the explanation for spontaneous bleeding when the prothrombin time is in the usual therapeutic range.

## Methods

Ninety studies were performed on 58 outpatients who had been taking warfarin for months or years. Four patients who completed a course of treatment were restudied after the warfarin had been discontinued. The blood was drawn during a routine clinic visit, and the patients were questioned and examined for bleeding problems at the same time.

For Quick prothrombin time determination in the hospital clinical laboratory, 4.5 ml of blood in 0.5 ml of 3.8 sodium citrate solution was used. The thromboplastin was Simplastin® (Warner-Chilcott). Percent activity was calculated from saline solution dilutions of pooled normal plasma.

For tests in the research laboratory, a second syringe (plastic) was filled with blood through the same needle and mixed with one-ninth volume of acid citrate anticoagulant<sup>9</sup> in a graduated polycarbonate centrifuge tube. The blood was centrifuged at once, the plasma transferred in portions to siliconed capped tubes and frozen at  $-30^{\circ}$  for

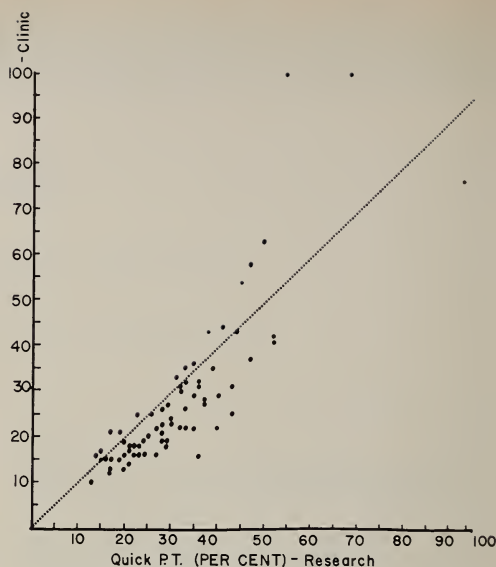


Chart 1.—Each dot compares the results of the one-stage Quick prothrombin time test on a single specimen as obtained in the research laboratory and in the hospital clinical laboratory. In this and subsequent charts the higher values were obtained on patients after warfarin therapy had been discontinued.

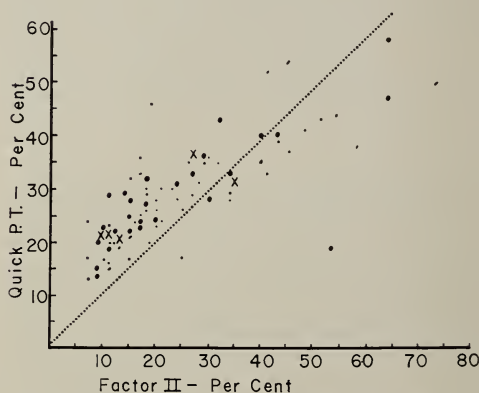


Chart 2.—Each dot compares the results of the Quick test with the Factor II assay on a single patient specimen. In this and in Charts 3, 4, and 5, the X's refer to values obtained on patients who were actively bleeding. The large dots refer to values obtained on patients who bled before or after the sample for testing was obtained. The small dots refer to values obtained on patients who did not bleed.



TABLE 1.—*Quick Prothrombin Times—Effect of Different Commercial Thromboplastins*

Patient No.	Rabbit Brain		Rabbit Brain and Lung	
	Seconds*	% Activity	Seconds*	% Activity
1	15	56	17	31
2	20	36	22	21
3	20	36	23	20
4	22	32	29	14
5	26	24	32	11.5
6	26	24	30	13
7	36	15	43	<10

\*Rounded off to the nearest whole second.

a maximum of two weeks before assay. Once thawed, the plasma was used within several hours or discarded. Serum for the thromboplastin generation test was obtained from 2 ml blood incubated in a new 12 x 75 mm glass tube for three hours at 37°C. It was also stored in the frozen state before testing.

For Quick prothrombin time determination in the research laboratory a saline solution extract of acetone-dehydrated human brain was used.

Factor II was assayed in a one-stage procedure,<sup>10</sup> using human brain thromboplastin and, as substrate, a mixture of equal parts of barium sulfate absorbed oxalated beef plasma and human serum completely deprived of prothrombin by clotting whole blood in the presence of silica powder (Celite-Analytical Filter-Aid, Johns Manville).

Factor VII was measured along with Factor X in a similar system, replacing the human serum with bentonite-absorbed human plasma.<sup>11</sup>

Assay of Factor X differed from assay of Factors VII and X by the use of Russell's Viper Venom in the place of brain thromboplastin.

Factor V was evaluated by the technique of Borchgrevink, Pool and Stormorken.<sup>12</sup>

Factor VIII was measured by a thromboplastin generation technique as previously described.<sup>13</sup>

Factors IX, XI and XII were assayed in a partial thromboplastin time system. For Factors IX and XII, the substrates were plasmas of congenitally deficient patients. An artificial substrate was used for the Factor XI assay.<sup>14</sup> Plasmas were activated with Celite for one hour.

For the partial thromboplastin time, cephalin prepared by the Bell and Alton method<sup>15</sup> was used. Plasma was activated with Celite for six minutes. Our normal range is 35 to 50 seconds.

The thromboplastin generation test employed cephalin, aluminum hydroxide-absorbed citrated plasma and serum in the incubation mixture. Out-

dated blood bank plasma (in acid-citrate-dextrose solution) was the substrate for the second stage. Normal plasma and serum reagents were tested each day, and always had a substrate clotting time less than 12 seconds after six minutes of generation.

## Results

The Quick prothrombin time was tested on the same plasma specimens in the hospital clinical laboratory and in the research laboratory. Despite the use of rabbit brain and lung thromboplastin in the former laboratory and human brain thromboplastin in the latter, results showed a significant agreement (Chart 1). There was a tendency for higher percent activities with the human thromboplastin; and, in individual cases, the decision as to the requirement for increased warfarin or for its antidote would have been radically different if the human brain data had been used rather than that from the clinical laboratory. Discrepancies in percent activity in the Quick time due to different thromboplastins have long been recognized.<sup>16</sup> Table 1 demonstrates this in an experiment performed a number of years ago but not previously published. The two commercial thromboplastins had identical clotting times when tested against saline dilutions of normal pooled plasma, but obviously could lead to quite different interpretations when tested on the plasma of anticoagulated patients, whether the results were reported in percent activity or seconds.

Factor II, or prothrombin concentration, was generally lower than the one stage prothrombin time test (Chart 2). In the therapeutic range of 20 to 30 percent for the prothrombin time, the Factor II concentration varied from 7 to 34 percent with 90 percent of the values in the 10 to 30 percent range.

Factor VII (SPCA) was even more depressed than Factor II (Chart 3). When the prothrombin

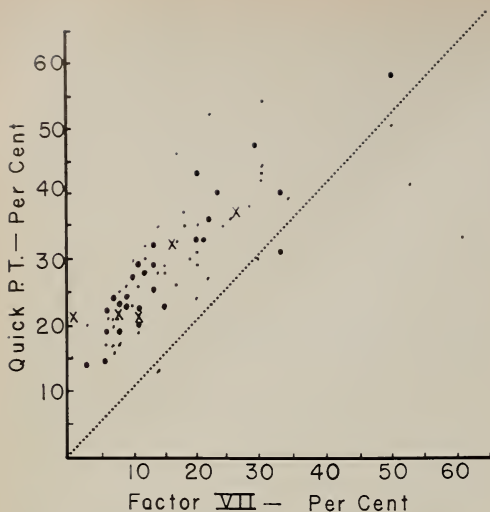


Chart 3.—Comparison of the Quick test with the Factor VII and X assay.

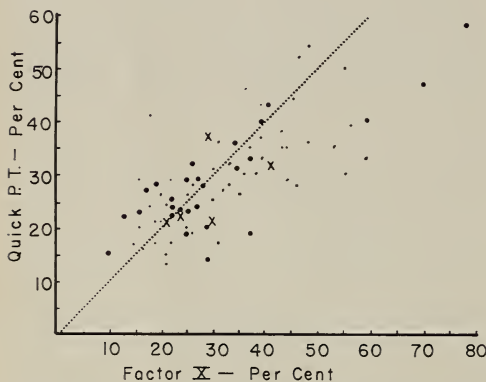


Chart 4.—Comparison of the Quick test with the Factor X assay.

time was in the therapeutic range Factor VII varied from 1 to 29 percent, and 90 percent of the values were 5 to 20 percent.

Although the Factor VII assay used is also sensitive to Factor X, a specific assay for Factor X, or Stuart factor (Chart 4) seemed to agree better with the prothrombin time. Ninety percent of the values of Factor X were in the 13 to 37

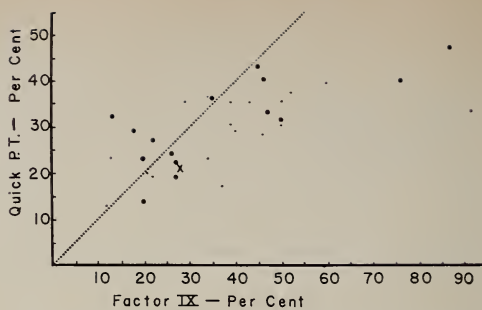


Chart 5.—Comparison of the Quick test with the Factor IX assay.

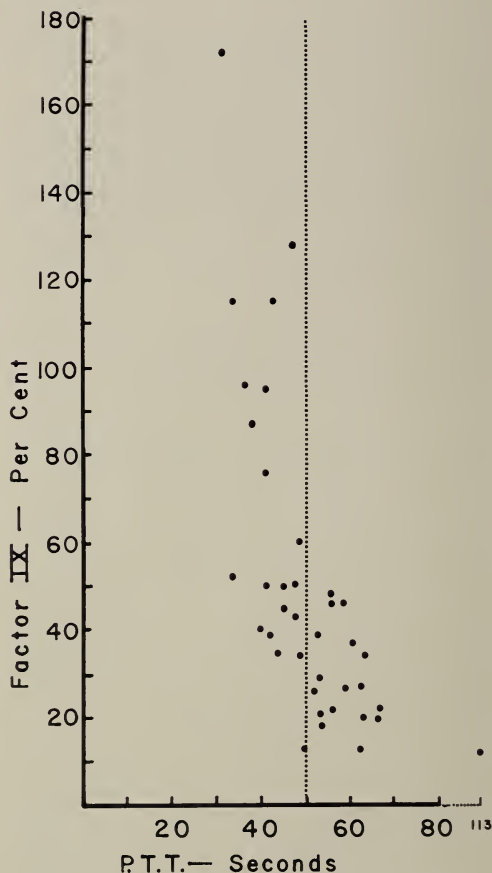


Chart 6.—Comparison of the partial thromboplastin time (prt) with the Factor IX assay.

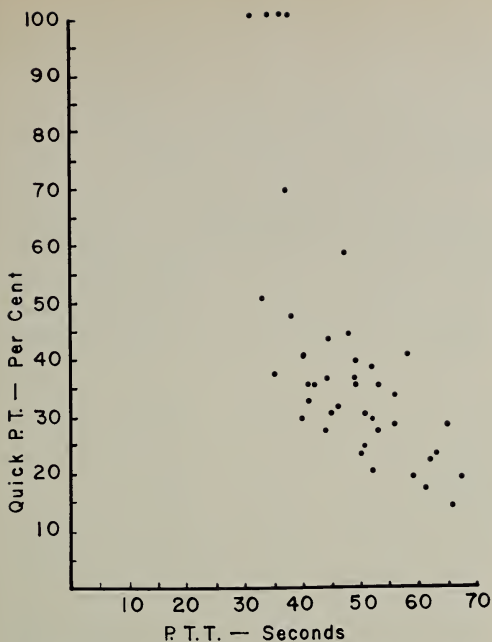


Chart 7.—Comparison of the PTT with the Quick test.

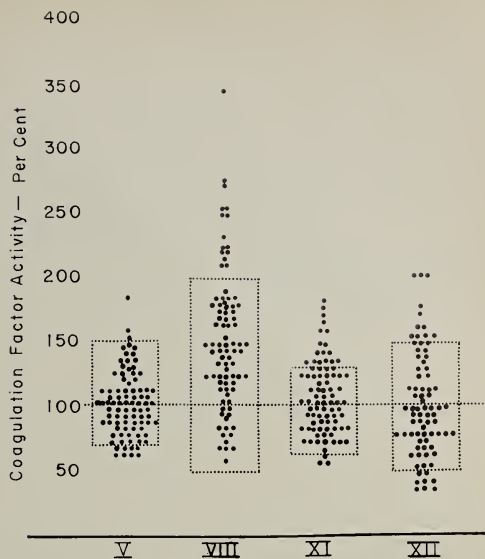


Chart 8.—Levels of Factors V, VIII, XI and XII. The rectangles outline the normal ranges.

percent range when the patient's prothrombin times were in the therapeutic range.

Factor IX (PTC) was not determined in all patients (Chart 5). It showed some correlation with the prothrombin time, but varied from it in a more unpredictable manner than the other factors. When the prothrombin time was in the therapeutic range, the Factor IX varied from 12 to 50 percent; and when the prothrombin time was in the 10 to 20 percent level, the Factor IX was 12 to 37 percent.

The partial thromboplastin time was investigated as a screening test for Factor IX depression (Chart 6). When Factor IX was under 30 percent the PTT varied from 50 to 113 seconds, but abnormal PTT's were seen with Factor IX levels as high as 47 percent. There seemed to be a better correlation of the PTT with the prothrombin time (Chart 7).

The thromboplastin generation test was abnormal in every patient under chronic warfarin therapy. The abnormality was confined to the patient's serum reagent. However, the defect in the thromboplastin generation test correlated very poorly with the Factor IX level, the Factor X level or the partial thromboplastin time.

Chart 8 shows the values obtained for levels of Factors V, VIII, XI and XII. In agreement with results reported by most previous investigators, these factors are not reduced by warfarin therapy, nor was there any evidence for a general compensating rise in these factors. Fifteen of the Factor VIII levels were above the upper limits of normal. Four of these patients were retested when anticoagulant therapy had been discontinued for more than a week, and two had returned to normal range.

Five patients were bleeding at the time blood was drawn for testing. The clotting values showed no tendency to be below the range obtained in the non-bleeding patients by any of the screening tests or factor assays (Charts 2 to 6). Twenty-nine studies performed on 13 patients who had bled before or after the withdrawal of test samples also showed no tendency to low values by any of the tests. Information on the patients who bled is outlined in Table 2.

## Discussion

In more than 50 percent of patients in this study who bled abnormally during chronic anticoagulant therapy, a local cause for bleeding was



	Actively Bleeding Patients	Site of Bleeding	Quick PT (Percent)	Local Cause
	A	Dental	21	Diseased gums
	B	GU	22	Stone
	C	GYN	32	Endometrial hyperplasia
	D	Epistaxis	21	None
	E	Epistaxis	37	None
	Patients Tested at a Time Remote from Bleeding	Site of Bleeding	Lowest Recorded Quick PT	Local Cause
	F	Dental	14	Postoperative
	G	Muscle	20	Scleroderma
	H	GYN	22	Proliferative endometrium
	I	GI and GU	23	Nephrotic syndrome (prednisone)
	J	GYN	24	Enovid
	K	Anal	28	Fissure
	L	Dental	28	Diseased gums
	M	GU and epistaxis	11	None
	N	Ear and epistaxis	15	None
	O	Epistaxis	19	None
	P	GU	22	None
	Q	Retroperitoneal	23	None
	R	GU	25	None

TABLE 2.—*Prothrombin Time (Quick) in Patients Who Bled*

evident. None of the five patients who were tested at a time when they were actively bleeding had a Quick prothrombin time value less than 20 percent. Although three of the remaining 13 patients who bled had prothrombin times below 20 percent, this proportion of low values was not greater than occurred among the non-bleeding patients. Moreover, none of the other tests performed provided results which would distinguish the bleeding patients.

The importance of local causes for bleeding in patients on long-term anticoagulant therapy has been stressed by other investigators. In Bjerke-lund's<sup>17</sup> series, 18 of 52 patients who bled had some explanation other than the anticoagulant. Usually the lesions in such instances are evident, but occult tumors must be sought.<sup>18</sup>

The data obtained with the study indicate that, for all its defects,<sup>19</sup> the Quick prothrombin time method remains a satisfactory technique for control of anticoagulant therapy with medication which depresses the levels of vitamin K-dependent plasma coagulant factors. No additional information of benefit could be obtained by specific assays for coagulation factors nor by use of the partial thromboplastin time or thromboplastin generation test.

Within limits, the levels of Factors II, VII, IX and X could be predicted from the Quick pro-

thrombin time. Levels of Factor VII would generally be expected to be significantly lower; levels of Factor II were somewhat lower; and levels of Factor X were approximately the same as the Quick values. Although Factor IX, as expected, correlated better with the partial thromboplastin time (which is influenced by Factor IX) than with the Quick test (which is not), there was no tendency for disproportionate depression of Factor IX or any other coagulation factor to correlate with bleeding. The relationship between coagulation factor levels and the Quick prothrombin time described here refers only to patients on chronic anticoagulant therapy. In the first few days of acute therapy, the Quick time primarily reflects Factor VII levels.

The thromboplastin generation test showed a poor correlation with all of the other tests. Most probably this reflects the varying states of activation and decay of Factor IX during the clotting of each specimen of blood<sup>20</sup> so that the Factor IX level resulting in the serum varied considerably.

There was a tendency for Factor VIII levels of these patients to be somewhat elevated. Although two of four patients returned to the normal range following discontinuation of therapy, it remains probable that Factor VIII elevations were a reflection of stress. Factor VIII rises with emotional disturbance and with tissue damage.

Voluminous data in the literature now indicate that the results of coagulation factor activity tests used to measure coumarin effect will vary widely with the test used and with the type of thromboplastin employed, whether results are reported in seconds or as percent activity. The therapeutic range desired can only be approximated by following published directions unless every aspect of the laboratory tests employed is identical. Each hospital has to establish the therapeutic range by a certain amount of trial and error. In the last analysis, each physician does this, unconsciously or otherwise, depending on the frequency of abnormal bleeding or thrombosis in patients under his care.

If agreement on a standard test and thromboplastin could be achieved,<sup>21</sup> patients would have far more uniform and successful care. Such agreement could be built around the Quick one-step prothrombin test, using acetone-dehydrated brain prepared according to the method of Quick.<sup>22</sup> The one advantage of thrombotest<sup>23</sup> is that it is a uniform reagent giving reproducible results from batch to batch supplied by a single manufacturer only. Similar results should be obtainable with a uniform Quick test and reagent.

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## ORAL CONTRACEPTIVES AND MONILIA

"When you use a combination oral contraceptive agent, you're more inclined to have monilia in cultures. This distressing side-effect—and it is distressing because it interferes with the normal coital behavior of the patient and her husband—is very difficult to treat if the patient is maintained on the combination agent, just as it is almost impossible to clear up during pregnancy. In such a patient, if you'll stop the medication, you can put her on a local estrogenic cream; and it by itself, without any anti-monilia agent, will clear up the infection. Or if the patient wishes to stay on oral contraceptives, you can treat her with an estrogen or an oral monilia agent and switch her over to a sequential type of oral contraceptive. You're more apt to get a cure and keep the patient on oral contraception."

—HOWARD BALIN, M.D., Philadelphia  
 Extracted from *Audio-Digest Obstetrics and Gynecology*, Vol. 16, No. 2, in the Audio-Digest Foundation's subscription series of tape-recorded programs.

# Quinton-Scribner Cannulas For Hemodialysis

## Review of Four Years' Experience

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AND JOHN R. DE PALMA, M.D., *Los Angeles*

■ *Data on a study group of 52 maintenance hemodialysis patients cannulated with Quinton-Scribner cannula in a four-year period were analyzed. The average period of dialysis was 11.8 months with either a pumped coil or a pumpless Kiil artificial kidney system. One hundred and forty-five cannulations were performed. The mean arterial cannula survival was 7.8 months and the mean venous cannula survival was 7.2 months. The exceptional longevity of cannula survival occurred despite the high incidence of atherosclerotic changes at operation and the advanced mean age (47 years) of the patients. The cannula longevity may be partially related to the technique used and to meticulous surgical care given the patient before and after cannulation.*

*Complications from cannulation included two deaths, one from septic pulmonary embolism of Staphylococcus origin, and one from acute Pseudomonas endocarditis. A total of 36 infections of cannulas were recognized, the majority being due to Staphylococcus aureus, but 28 percent being secondary to Gram-negative bacteria.*

SEMI-PERMANENT ARTERIOVENOUS cannula systems<sup>1,2</sup> have been the unique surgical contribution which has made maintenance hemodialysis possible. Since 1964, chronic hemodialysis has been conducted at Mt. Sinai Hospital in Los Angeles, and Quinton-Scribner cannula systems have been employed for all patients. This report summarizes the surgical procedures, problems, and significant

cannula complications for cannulations performed from November 1964 to December 1968, and includes data from the in-hospital program (coil, blood pump assist dialysis) and the home hemodialysis program (two-layer Kiil, pumpless system).

### Materials and Methods

Ninety-three uremic patients were cannulated during the study period. All cannula operations were performed by the first three authors and only

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TABLE 1.—*Age Distribution of Patients*

<i>Age (years)</i>	<i>No. of Patients</i>
<20 .....	1
20-29 .....	9
30-39 .....	11
40-49 .....	18
50-60 .....	13

one patient was lost to follow-up. By December 1968, the hemodialysis patient population totaled 37; each patient was hemodialyzed either in the hospital two or three times a week, or at home three or five times a week.

Twenty-four of the 93 patients were cannulated for treatment of acute rather than chronic renal failure, and ten for pre-transplantation dialysis. These latter categories of patients are excluded. The remaining 52 patients make up the study group and were dialyzed an average of 11.8 months (range 1 to 32 months). Each patient was dialyzed approximately 16 to 30 hours a week with either a two-layer Kiil or Travenol® twin-coil artificial kidney. One-hundred and forty-five arterial and venous cannulas were implanted in these patients during the four-year period.

Table 1 shows the age distribution of the 20 women and 32 men. Sixty percent of the patients in this program were over 40 years of age.

#### *Cannula Materials*

During the four years, several changes were made in the cannula equipment. In 1964 and 1965, teflon double-break shunts<sup>3,4</sup> were employed, with metal joint and crimp rings at the teflon-silastic union, and with cannula tips 4 cm in length. During 1966, the internal metal rings were replaced with fine ligature. The double-break teflon loop was replaced with a single-break male-female teflon connection. Cannula tips were shortened and tips of 2 to 2.5 cm have been used since mid-1966, with only 1 cm of the tip inserted into the artery or vein. Early in 1967, the single-break connection between the two silastic cannulas was changed to a single piece of teflon beveled at both ends.

#### *Surgical Considerations*

Preoperative clinical evaluation of the status of arteries and veins available for cannulation is critical. Presence of limb edema or of infection required temporary delay in operation. Absence

of pulses or veins, or obliteration of veins by previous phlebitis, eliminates the possibility of using that particular limb for cannulation, and rarely makes any cannulation impossible. Leg cannulas are preferred, especially for home-dialysis patients. The posterior tibial artery and the greater saphenous vein are usually used, but anterior tibial and peroneal arteries, and short saphenous and other superficial leg veins were also employed.

The surgical procedure was usually easier to perform on the arm, and that site was preferred for short-term use in cases of acute renal failure or pre-transplantation dialysis. The radial artery and any superficial vein 3 mm or larger in diameter are usually cannulated in these instances.

#### *Cannulation Technique*

Cannulations were done in an operating room under local anesthesia and light premedication. In this procedure the vessel to be cannulated is ligated with 4-0 Polydek® at its distal limit in the wound, and the ligature tails are used for traction. The caliber of the vessel is estimated, and a teflon tip\* of appropriate size (not the largest tip possible) is selected. The tip is shortened to 2 cm by cutting off the non-tapered end sharply; only 1 cm of the tip is inserted into the blood vessel. We believe the shortened tips reduce angulation problems.

This teflon-silastic union is secured with a single loop of 4-0 Polydek, tied snugly enough to indent the silastic. The silastic tubing must be selected from available 180° loops, reverse (360°) loops and straight pieces to suit the particular anatomic features of the vessel and cannulation site; care must be taken with leg arterial cannulas not to place them too distally lest gradual postoperative cannula egress, skin erosion or angulation occur.

A subcutaneous tunnel is developed to accommodate the silastic extension, and a small stab incision is made for percutaneous exit of the "step" portion of the tubing. Silastic tubing with "steps" is usually but not always employed.

A small incision is made in the vessel, usually cruciate in shape, to avoid rolling intima during tip insertion in arteries which may be brittle. Arterial bleeding is controlled by gentle traction of Polydek loops around the proximal portion of the artery. The cannula tip is then carefully inserted

\*Obtained from Extracorporeal and Medical Specialties Co., Inc., Mt. Laurel TWP, New Jersey. Teflon cannula tip sizes 18-13.

into the vessel, and is tied in place by one or two pieces of 4-0 Polydek. This insertion and fixation of the tip, particularly in the artery, is the most critical and most difficult step of the cannulation procedure, and an assistant may be required. The tails of the ligature on the distal vessel are tied snugly over the silastic tubing into which the teflon tip was inserted. These tails are then tied again, this time to the tails of one of the ligatures fixing the cannula tip in the vessel, forming a harnessing which prevents egress of the cannula from the vessel.

The cannula is then irrigated with heparinized saline solution. Blood flow rate from the arterial cannula is estimated. It is important that the cannula tip lie in the vessel without angulation, pressure or torsion from surrounding structures. Arterial cannula obstruction may occur if a flap of intima is pushed ahead of the teflon tip; it can be corrected by recannulation 1 to 2 cm cephalad. This complication can usually be prevented by avoiding the use of too large a teflon tip.

The vein is then cannulated in a similar manner. The arterial and venous cannula limbs are next connected by means of a 3 cm length of double-beveled teflon tubing. Flow through the shunt may be sluggish at first ("bubble-transit time" greater than three seconds) but it usually improves within minutes. Failure of rapid improvement in flow rate usually results in clotting within a few hours unless the obstruction is corrected.

Hemostasis is obtained with electro-cautery. Wounds are irrigated with 0.5 percent solution of kanamycin, and are closed by plastic technique with subcuticular 4-0 nylon. After closure, shunt flow is rechecked and the arteriovenous connection is bridged with Air-Vent® tape. The dressing is completed with a 4" Kling® roll.

#### *Postoperative Management*

Formerly plaster splinting was used to insure immobilization, but present practice is to elevate the cannulated limb and tell the patient not to move it. For leg cannulas, after three days of complete bed rest, wheelchair and crutches are allowed, with no weight-bearing on the cannulated limb for three weeks. Progressive ambulation is allowed thereafter. Cannulated arms are placed in slings for two or three weeks. Finger motion is encouraged to prevent muscle atrophy but wrist and forearm motion should be kept to a minimum during the first three weeks.

Preferably the dressing is not disturbed for five to seven days. Occasionally, however, a patient requires dialysis immediately following cannulation. Cannula displacement due to subcutaneous bleeding with dialysis in the early postoperative period can result in early cannula infection or failure. After the early postoperative period, cannula exit sites are cleansed before each dialysis with tap water and Betadine® or PhisoHex® or 3 percent hydrogen peroxide or 70 percent ethanol.

#### *Care of Cannula Complications*

Cannula problems usually are first seen and are resolved primarily by the dialysis nurses. Clotting and infection are the most common complications requiring special attention. Declotting, usually a nursing procedure, is carried out in the manner outlined by Pendras and Smith.<sup>5</sup> After declotting, cannula angiography<sup>6</sup> is obtained in anticipation of the need for cannula revision. Progressive deterioration of cannula function, often a forewarning of clotting, is recognized by diminution of arterial flow or by increase in venous resistance as measured during dialysis. Cannula angiography is performed to investigate such problems of cannula function. Heparin or warfarin are frequently used following cannula declotting, and anticoagulation is maintained until the underlying problem is resolved.

Purulent discharge at the point of insertion is routinely cultured. If infection is suspected, antibiotic treatment is begun immediately, often before the culture report is available. Overt cannula infection treatment requires a combination of hot, moist compresses, limb immobilization and elevation, and liberal use of appropriate antibiotics.

#### *Cannula Revisions*

Revisions are carefully planned to permit conservation of remaining unused arteries and veins for future cannulations. When possible, a new cannula tip is implanted one to two inches cephalad to the faulty tip site. However, in the presence of infection, particularly when cellulitis is present, new cannulation in a separate limb may be necessary. Segmental venous obstructions are often encountered during revisions. These characteristically occur as venous stenosis at the vessel-teflon tip or from 1 to 6 cm cephalad to the teflon tip. Occasionally, obstruction to flow will be

TABLE 2.—*Serious Complications of Cannulation in Series of 52 Patients*

Complication	No. of Patients
Severe infection of cannula requiring cannula removal . . . . .	8
Septicemia	
Staphylococcus aureus . . . . .	2
Pseudomonas (one death) . . . . .	2
Septic pulmonary embolism (one death) . . . . .	4
Arterial false aneurysm . . . . .	8
Bleeding, severe, requiring cannula removal . . . . .	2

TABLE 3.—*Organisms Identified in Cannula Infections*

Pathogen	No. of Cases
Staphylococcus aureus . . . . .	19
Staphylococcus epidermitis . . . . .	6
Staphylococcus albus . . . . .	1
Pseudomonas . . . . .	8
Klebsiella aerobacter group . . . . .	2

found entirely due to venospasm. Reliance is placed in such cases on preoperative cannula angiograms to help rule out mechanical obstructions.

## Results

Treating the 52 patients who were long-term participants in the dialysis program made up 49.5 patient-years of experience.

### *Transplantations, Deaths, and Transfers*

Of the 52 long-term dialysis patients, 16 died, 15 others left the program following renal homo-transplantation, and one transferred to another institution for care. Data concerning these patients' last cannula sets have been excluded.

The serious complications of cannulation are listed in Table 2.

Two deaths were due to sepsis, septic pulmonary embolism of staphylococcus origin in one case and acute pseudomonas endocarditis in the other. In each case a Quinton-Scribner cannula was the probable source of infection, as cultures of the circulating blood and of material from the infected cannulas were identical. The remaining serious complications of cannulas usually required the removal of the cannula system, except in one instance of a cannula exit site infection with staphylococcal epidermitis and associated septicemia. In this instance, cure was effected by long-term antibiotic treatment.

A total of 36 distinctly separate infections of Scribner cannulas were recognized in these pa-

CANNULA SURVIVAL, SCRIBNER SHUNTS

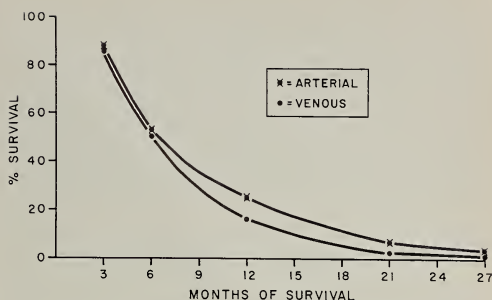


Chart 1.—Survival of Quinton-Scribner cannulas in 52 patients.

tients. The principal pathogens identified by culture in the clinical infections of cannulas are listed in Table 3.

Infections ranged from minimal inflammation to abscesses or severe cellulitis. Erythema without tenderness at the cannula exit sites was not a frequent early sign of infection in this study. Mild infections were also identified by tenderness about the implanted cannula or by purulent discharge around the tubing. At times, suppurative discharge was found only by "milking" the subcutaneous tunnel. Bleeding around cannulas was common but it reached serious proportions only twice, and in those instances cannula revision was necessary. Failure of response to treatment of cannula infection or further complication such as bleeding, false aneurysm or septicemia were considered urgent indications for cannula removal.

In two of the eight instances of pseudomonas infection, severe phlebitis eventually occurred. In these cases infections advanced from an insidious onset through a stage of minimal clinical findings, responded poorly to treatment, and progressed to septicemia resulting in acute endocarditis and death in one case and in septic pulmonary embolism, with recovery after cannula removal, in the other.

### *Cannula Survival*

For calculating cannula survival statistics, all functioning cannulas less than three months old were excluded. Seventy-two arterial cannulas implanted during the four-year period provide the material for calculation of survival data presented in Chart 1. Duration of cannula survival was cal-



culated from the date of cannula insertion. Mean arterial cannula survival was 7.8 months. However, 22 of the arterial cannulas included in these data were still functioning at the time the data were compiled. No significant difference in survival time ( $P>0.5$ ) was evident between arterial cannulas in the arm and those in the leg. Fifty-four arterial leg cannulas functioned an average of 7.7 months (range 1 to 27 months), while 18 arm cannulas survived a mean 8.0 months (range 3 to 26 months).

Chart 1 also shows the comparable venous cannula survival data. Mean survival for 73 venous cannulas was 7.2 months. Fourteen of the venous cannulas included were still functioning after periods of from 3 to 28 months at the time the data were compiled. A mean survival of 6.7 months (range 2 to 19 months) was obtained for 15 arm venous cannulas, as compared with 7.4 months (range 2 to 27 months) for 58 leg venous cannulas—not a significant difference ( $P>0.5$ ). There also was no significant difference ( $P>0.2$ ) between the mean survival of arm arterial cannulas (8.0 months) and that of arm venous cannulas (6.7 months).

## Discussion

Acute hemodialysis in man was first performed in 1943.<sup>7</sup> Treatment of patients in chronic renal failure became practical in 1960 with the development of the arteriovenous teflon shunt. The teflon cannula body and tip was replaced by a silastic cannula with teflon tip and this silastic teflon cannula system was reported in 1962 by Quinton et al.<sup>4</sup> The cannula experience of this newer system at the Seattle Artificial Kidney Center was reviewed in 1966 by Pendras and Smith.<sup>5</sup> In reviewing 47.6 patient-years cannula experience over a four-year period, they found cannula survivals of 14.3 months average for arterial (range 1.3 to 38 months) and 11.7 months for venous cannulas (range 1.3 to 51 months).

Other investigators, however, have been unable to duplicate the cannula longevity reported by the Seattle group. Cannula data presented by Rubini et al<sup>8</sup> indicated an average cannula survival time of 8.1 months for both arterial and venous cannulas in 16 patients treated an average of 15.6 months each. The ages of these patients were not given but since the patients were carefully selected from a large patient population by medical and

other criteria, it is probable that they had minimal or little peripheral vascular disease.

McDonald and associates<sup>9</sup> reported an average venous and arterial cannula life of 4 months and 4.8 months, respectively, in a total of 105 months' cannula experience with 11 patients. Less satisfactory results were obtained by Wilson et al<sup>10</sup> in 80 patients. They reported mean "shunt life" of 2.2 months in 39 patients without distinction between arterial and venous cannulas.

The mean cannula longevity in this report is remarkable considering the high mean age of the patient population (47 years) and the frequency of moderate to severe peripheral vessel atherosclerotic narrowing and changes seen at surgical operation. The most common cannula complications were infection and impaired blood flow due to stenosis, with resultant inadequate dialysis or clotting. Chronic infection, often subclinical for days to weeks, probably contributed to venous stenosis, arterial false aneurysm, and bleeding at the cannula exit site. The cannula exit sites are constant portals of entry for bacteria. We suspect that perivascular lymphangitis may be continuously present, and may account for the frequent findings of segmental venous stenosis and obstruction several centimeters cephalad of the teflon tip.

Frequently, other factors are associated with cannula failure. Underlying primary vascular disease (vasculitis, arteriosclerosis, phlebitis) has been present in some cases. Hypotension, hypovolemia or reduced cardiac output resulting from major abdominal operations or bleeding resulted in cannula thrombosis in three cases. In each of these cases of normal cannula function resumed on removal of the clot but cannula malfunction occurred subsequently, necessitating surgical revision within two months, possibly because of endothelial damage at the time of clotting.<sup>11</sup>

If the vessels available for cannulation are so small that the smallest cannula tip (No. 18) can be inserted only after forceful dilatation of the vessel, there is little hope for cannula longevity.

Some degree of manipulation of the cannula always is necessary during union with the artificial kidney. Since tugging and torsion upon the tubing contributes in some measure to cannula failures, it should be kept to a minimum by all personnel who handle the cannulas. Progressive irreversible egress of the subcutaneous portion of silastic tubing occurs with excessive manipulation.

Cannula materials *per se* have been indicated as a source of thrombosis. In our experience, only three instances of spontaneous clotting were found which were unrelated to significant cannula stenosis or obstruction of flow as seen on angiograms or at operation, and each of these exceptions was associated with acute hypotensive or hypovolemic states.

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#### PREMATURE LABOR AND DECREASED HEART SIZE

"A great number of premature labors occur unexpectedly, without recognizable etiology. It begins to appear that many of these may be on a circulatory basis. We and others have reported that patients with a decreased heart size during pregnancy have an increased chance of premature labor. With decreasing heart volume, there's a great increase in the rate of prematurity—1.5 percent in patients with a heart volume of 750 ml or more compared to 24 percent when it's below 350 ml. The small heart, probably associated with decreased cardiac output and a reduction of uterine blood flow, may result in a relative uterine hypoxia and myometrial irritability with subsequent onset of premature labor. It has been our experience, as well as that of others, that reduction of the work load of those patients with smaller than normal heart sizes will drastically reduce the anticipated high risk of prematurity."

—EDWARD BISHOP, M.D., Philadelphia  
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# Family Rubella Study in Los Angeles

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■ *A prospective study was initiated before the expected rubella epidemics in 1964 and 1965 in Los Angeles. Seventy-six families were evaluated by means of rubella complement fixing (CF) antibodies. The CF test, which has notable limitations, was chosen as a serologic test because it was possible to secure repeated samples of sera from all members of the families if venipuncture could be avoided.*

*Definite evidence of clinical or serological rubella occurred in 13 of 399 persons enrolled in 1964, an attack rate of 3.3 percent. Four persons had clinical rubella only, five had clinical disease with seroconversion and four had seroconversion only. The ratio of apparent to unapparent disease was nine to four.*

*There were four key families, each of which had more than one individual with definite clinical or serological evidence of rubella, suggesting that clustering of rubella cases does occur in families having an index case. In these families three types of intra-family spread were demonstrated: (1) all affected members had clinical disease, (2) all those affected had only inapparent disease, and (3) both apparent and inapparent disease in the same family.*

IN LIGHT OF THE FACT an epidemic of rubella occurred in the eastern and midwestern portions of the United States during the winter and early spring of 1964,<sup>1,2,3</sup> it was anticipated that the disease might reach epidemic proportions on the West Coast during that same spring. Therefore a pros-

pective study was initiated to investigate the frequency and spread of apparent and inapparent rubella in selected families in a circumscribed area of Los Angeles during the spring of 1964 and again in the spring of 1965, and to determine the complement fixing (CF) antibody response in members of these families. Though a major epidemic did not occur in Los Angeles, the data is being reported since it suggests clustering in families and points out that CF antibody response may not occur in infants and in some older patients.

We have been unable to find any similar report of a serological-clinical study of intra-family spread of rubella in the literature.

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Reprint requests to: Department of Laboratory Medicine, Mayo Memorial Building, Box 198, University of Minnesota, Minneapolis, Minnesota 55455 (Dr. Matsen).



## Methods and Procedures

### *Study Populations*

The families selected were mainly those of mothers who had previously enrolled in an ongoing investigation of the effect on the fetus of maternal virus infection during pregnancy, conducted in cooperation with the Southern California Permanente Medical Group in west-central Los Angeles. In addition, other families receiving health care from that group were included. A total of 84 families agreed to participate. Blood was obtained from all available family members in April and in June-July 1964 and June-July 1965.

The ideal family situation for purposes of this study was believed to be one in which there was at least one school age and one pre-school age child. Emphasis was placed on pre-school children in the belief that this age represented the largest pool of susceptibles, six years having elapsed since the previous epidemic of rubella in this area.

All families lived within a geographic area having a diameter of approximately seven miles and located in southwest central to northwest central Los Angeles. The geographic area included all major racial groups and covered the social-economic spectrum of lower to upper middle class.

### *Data Collected*

Parents were questioned regarding history of rubella in each member of the family. After initial enrollment in the study and during the anticipated epidemic period April-June, 1964, all families were contacted weekly by telephone to determine occurrence of any illness or rash, or known rubella exposure. All families were given a historical data sheet and asked to record dates and description of any illnesses. Telephone calls to remind parents about the continuing collection of historical data and to collect illness reports were made in the fall of 1964, in the winter of 1964-65, and in the spring of 1965.

At the time the specimens were obtained and data sheet collected, the physician making the family visit questioned the family as to the history of illness, pregnancy, outcome of pregnancy, and definite or suspected exposure to rubella.

The clinical criteria used for rubella diagnosis were: (1) posterior cervical or suboccipital lymph node enlargement, (2) a macular, pink-red morbilliform rash beginning on the head, neck or upper trunk, with subsequent rapid spread and usual dis-

appearance by the end of day three, (3) mild prodromal symptoms with very little or no coryza, and (4) little or no fever. Adults, it was realized, could manifest more severe involvement with arthralgia, myalgia, and more pronounced malaise. Presence of both rash and nodes was required for a clinical diagnosis in this study.

Blood specimens for complement fixation tests were obtained by finger-prick. Blood was allowed to absorb to saturation on three 1 mm thick absorbent paper discs, and then frozen at  $-70^{\circ}\text{C}$ . Complement fixation testing\* was carried out using the method previously described.<sup>4</sup>

Using sterile forceps, the three paper discs were placed in a 10 ml disposable glass syringe. One ml of Veronal® (5, 5-diethylbarbituric acid) buffered saline solution was added, and the plunger was inserted in the syringe only enough to be in position. The plastic tip was then removed from the syringe, and, using the plunger and with the tip-end upward, all air was removed from the syringe, and the tip replaced. The discs were left in the diluent to soak overnight with the syringe in a horizontal position at  $4^{\circ}\text{C}$ . Using the plunger, the diluent was squeezed from the discs into a 12x75 mm tube. The syringe and discs were discarded at this point. The blood dilution was inactivated at  $60^{\circ}\text{C}$  for 30 minutes, in order for the heat to coagulate any unlysed cells and paper disc debris. The diluent was next centrifuged at 2,500 to 3,000 rpm for 15 minutes in a refrigerated centrifuge to remove any coagulated material. The supernatant was poured into a sterile 1 dram vial. A complement fixation test was either performed immediately, or the serum was stored temporarily at  $-20^{\circ}\text{C}$ . The test was read without difficulty provided all the debris had been removed.

## Results

### *Frequency of Complement Fixation Titers of $\geq 4$*

Of the total series of 399 persons for whom tests on initial sera are available, 18.2 percent had a complement fixation titer of  $\geq 4$ , the frequency in females being essentially the same as that in males. The lowest incidence was found in the children under five years of age (3 percent), while in those between 5 and 21 years about 14 percent had such a titer. In the adults, 35 percent had positive

\*Serological studies completed at Serology Laboratory, Perinatal Research Branch, National Institutes of Health, Bethesda, Maryland. We acknowledge the assistance of Mrs. Anita C. Ley, who is in charge of the Serology Laboratory.

TABLE 1.—Race and Family Size

	Number of:	Caucasian	Negro	Oriental	Mixed	Spanish-American	Total
Families	.....	38	24	3	3	8	76
Individuals	.....	186	134	17	17	45	399
Indiv./Family	.....	4.9	5.6	5.6	5.6	5.6	5.1

TABLE 2.—Family Size, Age of Members, Occurrence of Rubella

No. in Family	No. of Families	Total No. Indiv.	Family Size vs. Age of Members				No. of Families			R only	R + SC	SC only	Total
			Children ≥ 5 yrs.	Children < 5 yrs.	Parents		Children		Both > 5 + < 5				
					Father	Mother	All ≥ 5	All < 5					
3	2	6	1	2	1	2	—	1	1				—
4	23	92	13	34	22	23	1	12	10				—
5	27	135	35	47	26	27	1	6	20	1	1	1	3
6	13	78	25	27	13	13	1	—	12				—
7	7	49	19	16	7	7	—	—	7	2	3		5
8	2	16	6	6	2	2	—	—	2			3	3
9	0												
10	0												
11	1	11	7	2	1	1	—	—	1	1	1		2
12	1	12	6	4	1	1	—	—	1				—
Total	76	399	112	138	73	76	3	19	54	4	5	4	13

R — Clinical Rubella

SC — Seroconversion

titer, with the frequency in females being slightly greater than for males (39 percent against 31 percent). This difference was greatest in the age group 30 to 39 years (females 43.5 percent, males 22.5 percent). Correlation between a positive titer and previous history of rubella was very poor in adults and improved in children as age lessened.

#### *Incidence of Apparent and Inapparent Rubella*

Clinical and serological data are available for analysis for a total of 76 of the 84 families enrolled. Table 1 shows the distribution by race and family size. The Caucasian families (50 percent of total) averaged 4.9 members, the remainder 5.6.

Of the 399 persons studied, 138 were under five years of age, 112 were children between ages 5 and 21 years, 149 were adults, all parents and all over 21 years old (Table 2). Of the 76 families, 54 had both pre-school and school age children—that is, under five years and five or over. In 19 families all children were under five, but in at least half of these families one child attended nursery school or kindergarten. In only three families fathers did not participate.

Evidence of clinical or serological rubella or both occurred in 13 of 399 persons enrolled in 1964 (Tables 2 and 3, and Chart 1—Group I). This gives an overall attack rate of 3.3 percent. Of the 13 infected, four had clinical rubella only,

TABLE 3.—Seroconversion (sc) in Relation to Rash (R) 1964 Data (See also Chart 1)

Family No.	Age	GROUP I		
		R only	R + SC	SC only
86	13 yr. 6 mo.	<4-<4	<4-8	
13	7 yr. 6 yr. 4 yr. 4 yr. 17 mo.		<4-8 <4-8 <4-8 <4-4 <4-<4	
73	9 yr.		<4-8	
74	7 yr. 4 yr. 12 mo.			<4- 8 <4- 8 <4-16
80	34 yr. 6 yr. 3 yr.	<4-<4		(<4- 4) ? sc <4-16
GROUP III				
3	28 yr.			(<4- 4) ? sc
10	35 yr.			(<4- 4) ? sc
30	29 yr.			(<4- 4) ? sc
49	35 yr.			(<4- 4) ? sc

five had clinical disease with serological conversion and four had seroconversion only. The ratio of apparent to inapparent disease was nine to four. The four individuals who had only clinical rubella are included in the overall incidence figures, because it was felt that the seroconversion of at least

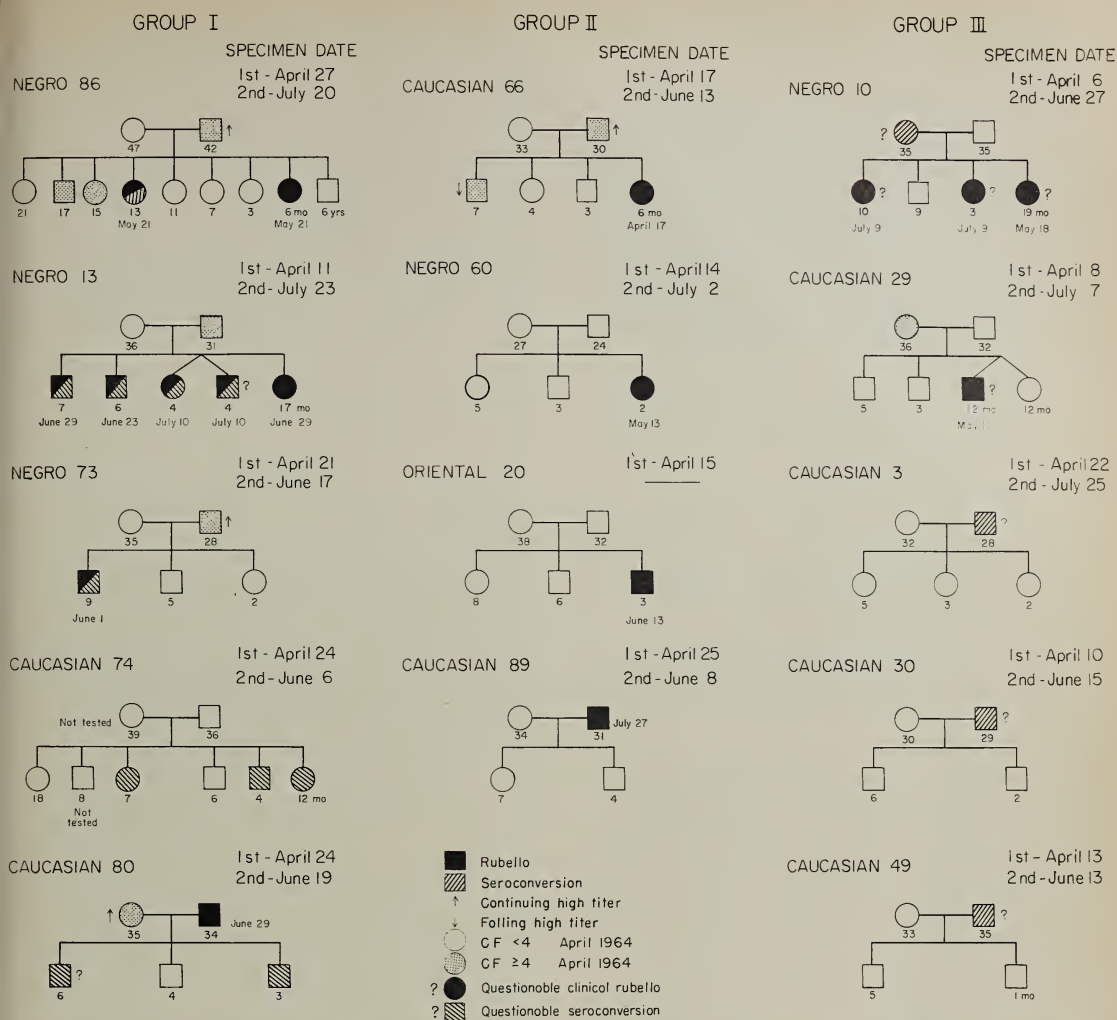


Chart 1.—Data on Clinical Rubella and Seroconversion for the Disease within 14 Families in Study Conducted in 1964.

one member of the family near the time of illness significantly enhanced the probability of the clinical diagnosis.

Group II in Chart 1 comprises four families, each with one individual having clinically diagnosed rubella without serological confirmation. In the three young children, serum specimens were properly bracketed to have revealed serological change if it had occurred. In the adult, the disease occurred after the second specimen of serum was collected. No apparent or inapparent infection was present in other family members. These four per-

sons are not included in the overall incidence total, since clinical diagnosis of rubella is difficult even by experienced physicians. Without the enhanced probability associated with an epidemic or concurrent seroconversion of the individual or a family member, the diagnosis in these cases was felt to be probable, but not definite.

Group III in Chart 1 contains five families with questionable serological or clinical rubella in one or more members. In one family questionable infection occurred in four members. Two infants (12 and 19 months) had possible disease. In one



instance, the father of the 19 month old had a serological change from less than four to four only.

### *Evidence of Clustering of Rubella in Families*

In four of five families (Chart 1, Group I) more than one member had definite clinical or serological evidence of rubella. In these four families three types of intra-family spread of rubella were demonstrated: (1) all persons affected had clinical disease (Families Nos. 86 and 13); or (2) all affected had only inapparent disease (Family No. 74), and (3) both apparent and inapparent disease occurred in the same family (No. 80).

In order to determine whether the clustering which occurred in these families was greater than expected due to random distribution, Chi-square test of randomness based on Poisson variability<sup>5</sup> was performed.\* This test was applicable only to family sizes of five, seven and eight and was found to be significant at 2.5 percent level in the family size of five, 0.1 percent in the family size of seven, 8 percent in the family size of eight.

### *Serology Sampling in June-July, 1965*

There were no serologically proven cases of rubella found in the analysis of 1965 specimens.

## **Discussion**

Naturally occurring rubella usually results in rise in complement-fixation (CF) antibody, the titer appearing several days after the disappearance of the rash and beginning to decrease 8-10 months later.<sup>4</sup> Only half of a series of female adults of childbearing age had detectable antibody levels and these were low.<sup>6</sup> In congenital rubella, CF antibody response usually appears late, if at all.<sup>6,7,8</sup>

Utilizing neutralizing tests to determine susceptibility, experimental studies in children demonstrated that the disease developed in one of five susceptibles on single brief contact, and 11 apparent and five inapparent illnesses followed prolonged or repeated exposure.<sup>9</sup> Similar findings are reported in respect to natural rubella in institutionalized children<sup>10</sup> and in adults (army recruits) following exposure to an index case.<sup>11</sup> In the present study, the fact that many family members escaped both clinical rubella and CF antibody conversion illustrates a rather low communicability of rubella.

Why seroconversion did not occur in a six-month-old and a 17-month-old infant with clinical disease is not clear. Older children with clinical rubella in these families did have conversion (Table 3 and Chart 1, Families 86 and 13). However, the 34-year-old parent in Family 80 (Table 3) also did not have seroconversion. Seroconversion did occur in a 12-month-old infant in Family 74 and in the three-year-old in Family 80. In this latter family, the index case may have been the three-year-old, the next infected the six-year-old (seroconversion only) and finally the mother who was the only one who had a rash.

The complement fixation test was chosen as a serologic test for antibody to rubella because it was possible to secure repeated specimens of sera from all members of the families if venipuncture could be avoided. An obvious disadvantage is the lack of information regarding previous immunity due to the fact that rubella CF antibodies decline and may disappear months or years after primary infection has occurred (unlike the hemagglutination inhibition antibodies). Further, it has been subsequently shown<sup>12</sup> that there may be no CF antibody response at all in some patients. The incidence of CF titer in this study is similar to that in other series<sup>6</sup> although the level appears higher for females of the childbearing age. In a number of patients without history of immediately antecedent infection an antibody level of 8 to 16 was reported. The CF results on sera taken from certain mothers in this study population, during their participation in the previously mentioned continuing study of virus in pregnancy, revealed fluctuation in the rubella CF level during the period between 1959 and 1964 without known infection or exposure to rubella. For example, in one mother from 1960 to 1962 titers were 16, 8, 4 and 16; in another over a five-year period titers were 0, 8, 0, 8, 0 and 8; and in another there was no change, all titers being 8 throughout. The current interpretation is that a titer level of 8 or more on a single specimen suggests (but does not prove) recent infection.<sup>4</sup>

## **Conclusion**

This study suggests that clustering of rubella cases does occur in families having an index case. Examples of three types of intra-family spread have been presented, (1) all affected individuals had clinical disease, (2) all those affected had only inapparent disease, and (3) both apparent and inapparent disease in the same family.

\*Courtesy of Alan Forsythe, Ph.D. and Coralee Yale, Division of Biostatistics, Department of Preventive Medicine and Public Health, UCLA, for statistical analysis (Health Sciences Computer Facility sponsored by National Institutes of Health Grant No. F.R. 3).

Complement fixation seroconversion failed to occur in certain infants with clinical disease whose siblings had serologically confirmed clinical rubella. That a CF antibody response may not develop despite clinical disease has been reported previously. Reasons for this are unclear.

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#### Correction

#### Rubella—Hemagglutination-Inhibition Tests

Through typographical error, misinformation that could cause serious difficulties in laboratories was contained in the paper, "Rubella—Technical Problems in the Performance of Hemagglutination-Inhibition (HI) Tests," which was published in the November 1969 issue. On page 353 in the section entitled "Conditions of incubation of the tests" the first sentence reads: "Rubella hemagglutination occurs optimally at 40°C . . ." This should have read 4°C, rather than 40°C.

The manuscript was correct; the error was made in typesetting and proof-reading.

# CASE REPORTS

## Atrial Myxoma Manifested as Cerebral Vascular Disease

FREDERICK A. JORDAN, M.D., IRENE O. GLEASON, M.D., AND MYRON FELD, M.D.,  
*Long Beach*

PRIMARY CARDIAC TUMORS are found in 0.05 percent of routine autopsies. Fifty percent of all intracavitary tumors are myxomas, and 75 percent of these occur in the left atrium.<sup>1</sup> In approximately 25 percent of the cases of left atrial myxoma, the presenting symptoms and signs are limited to the central nervous system, and in about 33 percent, the CNS manifestations predominate to the extent of obscuring the cardiac abnormalities. The central nervous system involvement is due to the friability of myxomas, with resulting cerebral embolization.<sup>2</sup>

The antemortem diagnosis of intracavitary cardiac myxoma was not correctly made until 1950, when Goldberg<sup>3</sup> used angiocardiography to demonstrate it in a three-year-old boy. In 1954, a tumor of this kind was successfully removed for the first time.<sup>4</sup> Angiocardiography and cineangiography establish the diagnosis with relative certainty, and owing to the benign nature of myxomas there is reasonable chance of complete cure with surgical removal.

This tumor can simulate a number of clinical entities such as thromboembolism secondary to myocardial disease; rheumatic heart disease with

mitral stenosis; subacute bacterial endocarditis; Stokes-Adams syndrome; and cerebral vascular disease.

### Report of a Case

A 68-year-old Filipino, a retired laundry worker, was admitted to the Long Beach Veterans Administration Hospital 4 December 1967 after falling and striking his head, with subsequent vomiting and urinary and fecal incontinence. On admission the head was noted to be "turned to the right" and the blood pressure was 200/150 mm of mercury. Past history included hypertension of unknown degree and duration, and an episode on 19 September 1967 of sudden onset of left hemiparesis. An electrocardiogram taken at that time had revealed only sinus tachycardia, and urinalysis had shown 1 plus albuminuria and microhematuria. The patient then had gradually improved and was discharged one month after admission "with weakness and some difficulty in walking." This condition had remained unchanged until the present admission.

Physical examination revealed blood pressure of 170/90 mm of mercury. The patient was alert and cooperative, but weak, and complaining of abdominal pain, nausea and vomiting. Crepitant rales with increased tactile fremitus were noted in the right lung base. Cardiac rhythm was regular with a point of maximal impulse in the sixth left intercostal space at the midclavicular line. There were no murmurs heard in the sitting position. The peripheral pulses were intact in all four extremities. A neurological examination showed right central facial weakness, a moderate weakness of all extremities, worse on the right and more pronounced in the arm, brisk deep tendon reflexes, and an extensor toe sign on the right. On lumbar puncture opening pressure was 220 mm of water and closing pressure was 120 mm. The cerebrospinal fluid was clear and slightly xanthochromic with sugar content of 129 mg, chlorides 750 mg and total protein 102 mg per 100 ml, a slight

From the Psychiatry and Pathology Services, Veterans Administration Hospital, Long Beach.

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Reprint requests to: Veterans Administration Hospital, 5901 East Seventh Street, Long Beach, Ca. 90801 (Dr. Jordan).



increase in globulin, no white blood cells and 110 crenated red blood cells. The colloidal gold curve was 000121000. An electrocardiogram showed sinus tachycardia with Q waves in leads 2, 3 and AVF suggesting an old inferior myocardial infarction, and borderline left ventricular hypertrophy. An electroencephalogram showed diffuse activity below the usual range of frequency and a focus of theta activity in the left temporal region. X-ray films of the chest and skull, a routine hematological work-up and urinalysis were normal except for slight albuminuria.

On 7 December 1967 the patient was lethargic but sitting up. The deep tendon reflexes were brisk and equal bilaterally. Hoffman and Babinski signs were absent bilaterally. On lumbar puncture on 13 December opening pressure was 240 mm of water and closing pressure was 110 mm. The cerebrospinal fluid was clear but slightly xanthochromic, with a sugar content of 77 mg, chlorides 665 mg and total protein of 110 mg per 100 ml, and a slight increase in globulin. A brain scan performed 18 December, using 10 ml of Technetium 99-m, revealed an abnormal uptake in the anterior view on the left, of a configuration seen with a subdural hematoma. An echoencephalogram showed no shift of the midline structures. Four days later a brain scan with 10 ml of Technetium 97 revealed no clearcut abnormality, although uncontrollable movements by the patient impaired the study.

A repeat neurological examination on 15 December showed generalized weakness, most pronounced in the right upper extremity, brisk 2 plus reflexes throughout, and flexor toe signs bilaterally. On 2 January 1968 the patient became somnolent. Nasogastric feedings were instituted, and methylphenidate (Ritalin®), 10 mg three times a day, was given. The patient was then noted to have moderately severe right central facial and bilateral upper extremity weakness. An echoencephalogram showed a right to left shift of 2.5 cm. A right carotid angiogram showed "extensive atherosclerotic changes in the right internal carotid artery with total occlusion of the right middle cerebral artery distal to the takeoff of the lenticulostriate branches, with perfusion of this area collaterally from the anterior cerebral artery" (Figure 1).

A lumbar puncture on 2 January showed an opening pressure of 95 mm of water, a closing pressure of 85 mm and crystal clear cerebrospinal fluid. The patient did not improve. Terminally,

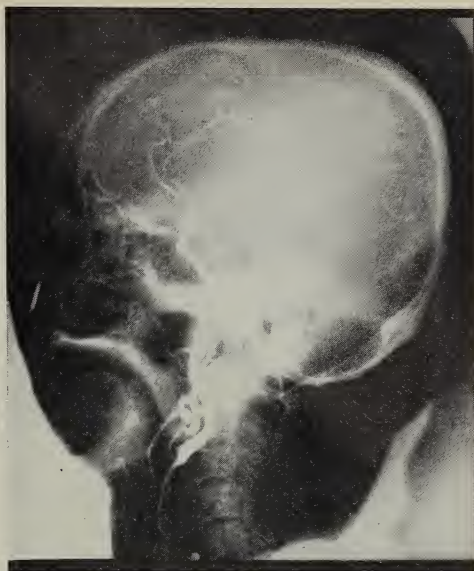


Figure 1.—Right carotid angiogram with no filling of middle cerebral artery.

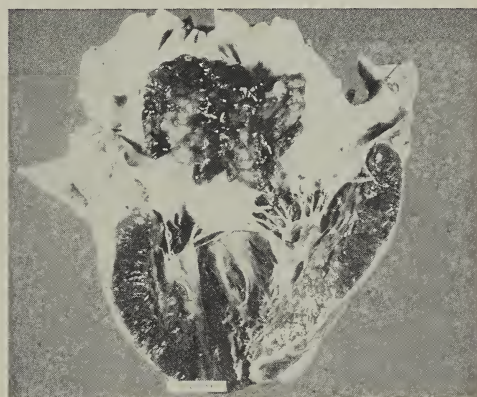


Figure 2.—Papillary myxoma attached to rim of fossa ovalis of left atrium (gross).

he became febrile, corneal reflexes were absent, and respirations were labored, with wheezes and rhonchi. He died 16 January.

### Pathological Findings

**Cardiovascular:** The heart weighed 500 grams and was slightly enlarged. The epicardium over the posterior-inferior surface of the left ventricle



Figure 3.—Myxoid stroma of tumor with vascular channels. Masson's Trichrome stain ( $\times 125$ ).

was slightly depressed and had a semi-translucent white appearance. The right ventricular myocardium was 0.4 cm thick, the left 1.5 cm. The left atrial lumen was slightly enlarged. Attached to the inferior rim of the fossa ovalis by a stalk 0.8 cm in diameter and 0.2 cm long was a glistening, translucent, gelatinous, yellowish-tan, polypoid tumor measuring 7 cm by 5 cm by 2.5 cm (Figure 2). The mass completely filled the chamber. The posterior papillary muscle and adjacent posterior inferolateral wall of the left ventricle revealed focal scarring of the myocardium. Microscopically, the tumor was seen to be attached to the endocardium by a short collagenized stalk in which were some muscular thick walled small arteries. The stalk as well as the tumor revealed foci of old and recent hemorrhage. The neoplasm was made up of papillary fronds. Within a pale bluish-pink edematous myxoid stroma, vascular channels were seen (Figure 3). Some of these contained blood, others appeared collapsed. Scattered throughout the intervening stroma were clusters of both round and fusiform cells. The former were surrounded by abundant amphophilic cytoplasm with either distinct cell boundaries or indistinct cell boundaries fusing with the matrix. The fusiform cells tended to occur in clusters or in linear rows suggestive of abortive vascular channels. In a few areas both cell types were surrounded by a vacuolated "halo." Pigment-laden macrophages as well as lymphocytes and mononuclear cells were present focally in the lateral areas. A few polymorphonuclear cells were seen in fresh hemorrhagic areas. The margins of the papillary fronds

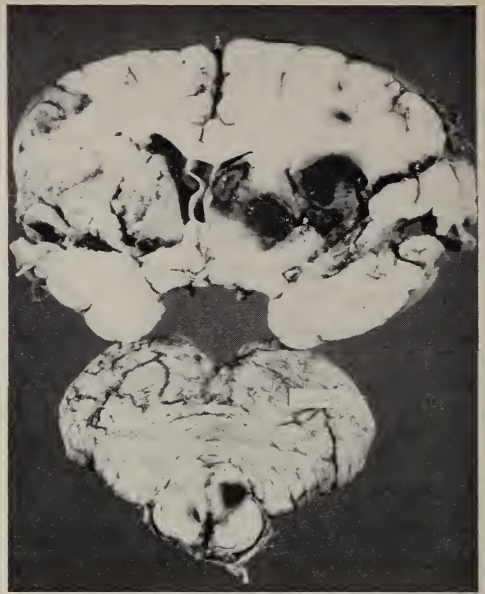


Figure 4.—Sections of cerebrum and brain stem showing anemic and hemorrhagic infarcts of the midbrain, basal ganglia, and contiguous structures (gross).

tended to be hypercellular and composed of the numerous round and to a lesser extent fusiform cells described previously. Multiple sections of the left ventricular myocardium revealed healing foci of muscle necrosis. Many small arteries within these foci contained tumor emboli with morphological characteristics of the left atrial tumor.

The brain weighed 1,570 grams. It was moderately edematous with some flattening of the gyri. Multiple necrotic and hemorrhagic areas were seen scattered over the cortical surfaces. The largest of these involved the right occipitoparietal area including the middle one-third of the post central gyrus. This lesion was roughly elliptical and its surface dimensions were 7 cm by 4 cm. Coronal sections revealed extension of the necrotic area 1 to 2 cm into the cerebral cortex and underlying medulla. Several other large hemorrhagic infarcts, recent and old, were evident (Figure 4). The major ones involved the left basal ganglia and internal capsule, the right lenticular nuclei, external capsule, claustrum, extreme capsule, and caudate. Sections through the brain stem revealed a 1 cm hemorrhagic lesion in the left inferior cerebellar peduncle and many diffusely scattered petechial hemorrhages. The circle of Willis contained



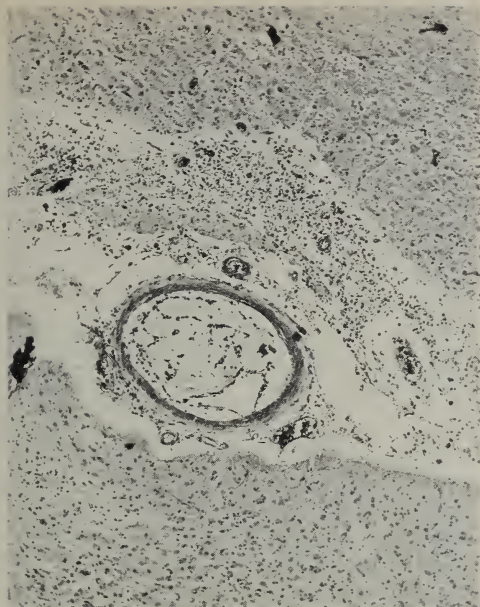


Figure 5.—Section of brain revealing tumor embolus in a small cerebral artery with an organizing adjacent infarct. Hematoxylin and eosin stain,  $\times 125$ .

patchy moderate atherosclerosis of its major arteries, and the right middle cerebral artery was completely occluded by a grey embolus.

Microscopically, the brain showed multiple areas of old and recent hemorrhagic infarcts with encephalomalacia. Many of the small arteries supplying these areas contained tumor emboli (Figure 5). The right middle cerebral artery revealed a tumor embolus completely occluding its lumen.

The liver, spleen and kidneys revealed tumor emboli, with infarcts in the latter two organs.

## Discussion

The first evidence of an intracavitary left atrial tumor in this patient was a cerebral vascular accident consisting of the abrupt onset of left hemiparesis requiring a month in hospital. Two months after the original episode he had recurrence of acute symptoms of cerebral infarction. The history of hypertension and the finding of xanthochromic cerebrospinal fluid led to the assumption that the two cerebral infarctions were due to hypertensive cerebrovascular disease. The patient's failure to improve clinically led to the consideration of a possible subdural hematoma but the true na-

ture of the patient's disease did not become evident until postmortem examination. The antemortem diagnosis of myxoma was not considered in this patient for several reasons: He was in the age group characteristic of cerebral vascular disease, he had preexisting hypertension, xanthochromic cerebrospinal fluid was found and there were no significant cardiac findings to alert the clinicians. In most instances, however, there will be clues suggesting the underlying disease.

Most of the patients with left atrial myxoma presenting with central nervous system symptoms have concomitant findings suggesting rheumatic heart disease with mitral stenosis or insufficiency. In 22 of the 33 cases reviewed by Silverman and coworkers,<sup>2</sup> when embolization occurred the brain was involved. The age range of the patients was from 3 to 66 years with a predominance in the 30 to 50 range. Characteristically, there was cardiac failure poorly responsive to treatment, with signs and symptoms of mitral stenosis or insufficiency. Many of the tumors reported have been accidentally discovered at mitral commissurotomy for intractable heart failure believed due to mitral stenosis from rheumatic disease. In those cases complicated by embolization the source of emboli was thought to be mural or valvular.

Apparent mitral stenosis without antecedent rheumatic fever, although a not infrequent occurrence, should suggest the possibility of atrial tumor, as should sudden signs of embolization without an obvious cause. Joint pain may occur in both conditions, as tumor emboli to the periphery may produce arthralgias.

Symptoms produced by the movement of a pedunculated tumor are the most important clues to its presence. A change in body position may produce the sudden onset of syncope, presumably due to obstruction of the mitral valve orifice and a resultant decrease in cardiac output. Accentuation of the pulmonary second sound indicative of pulmonary hypertension may be present. A long diastolic rumble heard at the apex, with or without presystolic accentuation, indicates mitral valve obstruction. If the rumble is heard in either the upright or supine position but not in both, it is very suggestive of myxoma in the left atrium. Occasionally there is a blowing systolic mitral murmur indicating regurgitation. A high gradient between the left atrial pressure and the left ventricular end-diastolic pressure may cause the mitral valve to open abruptly, with an opening snap. The



stream of blood that rushes from the atrium into the ventricle may cause the tumor to strike against the mitral valve leaflet and likewise produce an opening snap in the presence of a normal mitral valve.

With the aid of phonocardiography and careful auscultation one may elicit deviations from the classical findings of mitral stenosis which are suggestive of left atrial myxoma. These include the following: Diastolic and presystolic murmurs which are not as loud and prolonged as might be expected from the hemodynamic derangement and severity of the disease; marked changes in the character and intensity of the murmur with shifts in body position, and variability of murmurs from one examination to another; atypical location of the opening snap (whereas in mitral stenosis the opening snap is usually best heard in the third and fourth intercostal space at the left sternal border, in atrial myxoma it may be heard over the entire precordium or localized in the fifth intercostal space at the anterior axillary line); the appearance of previously undiscovered murmurs of mitral stenosis in patients with congestive failure.<sup>1,5</sup>

Peripheral embolization is common in mitral stenosis with atrial fibrillation. If embolization occurs in the presence of normal sinus rhythm, the possibility of atrial tumor should be considered. Anemia, accelerated erythrocyte sedimentation rate, increased serum gamma globulin and decreased albumin, increased C-reactive protein, serum lactic dehydrogenase, transaminase, and glutamic oxaloacetic acid are also frequent findings in the presence of this tumor, and these changes disappear with its resection.

The electrocardiogram is of no help in distinguishing the tumor from rheumatic mitral stenosis; nor are conventional x-ray films of the chest of significant value. The left atrium, in the presence of tumor, is nearly always normal in size or only slightly enlarged. However, the finding of a small left atrium in the presence of severe "mitral stenosis" should arouse some suspicion.

Cardiac catheterization may reveal data typical of mitral stenosis, with a significant gradient between the left atrial pressure and a simultaneously determined left ventricular and diastolic pressure. Cardiac catheterization also involves the risk of dislodging emboli. Several investigators<sup>6</sup> have noted that in combined left heart catheterization, phonocardiography and cineangiocardiography, the electrocardiographic timing signal on the cine-

radiographs permits correlation of heart sounds and pressure waves with movement of the tumor between the left atrium and left ventricle. In early systole the tumor suddenly moves from the left ventricle to the left atrium with the production of a large atrial v wave, a notch in the rising left ventricular pressure, a prominent c wave and loud late elements of the first sound.

In early diastole the tumor moves rapidly through the mitral valve, causing an abrupt diminution in the left atrial volume and rapid ventricular filling, resulting in a rapid y descent despite severe obstruction of the mitral valve. An early diastolic sound thought to be an opening snap may be related to the checking of the tumor in the left ventricle ("tumor plop"). The pressure phenomena recorded at left heart catheterization are quite different from those seen in typical rheumatic mitral stenosis. A tall v wave and a rapid y descent in left atrial myxoma have been described by other investigators.<sup>7-12</sup> These findings, usually attributed to mitral incompetence, are noted with left atrial myxoma in the absence of clinical or angiographic evidences of mitral incompetence. A notch on the left ventricular up-stroke similar to one seen by Pitt et al<sup>6</sup> has been demonstrated. This may result from the left ventricle contracting with a large volume (tumor and blood), then undergoing a sudden release of tension before aortic valve opening, with the tumor being propelled into the left atrium. This release of tension results in a notch and change in slope of the left ventricular pressure curve. Several observers have postulated that the notch will occur only in cases in which the tumor passes through the mitral valve. The presence of a notch and change in the upslope on the left ventricular pressure curve indicates a left atrial tumor, though their absence does not rule it out.<sup>6</sup>

## Summary

A patient with history of cerebral vascular accident was admitted to hospital with acute symptoms of cerebral infarction. Spinal fluid was xanthochromic. Subdural hematoma was considered when the patient did not improve but not until postmortem examination was atrial myxoma diagnosed.

The antemortem diagnosis of cardiac myxoma, formerly of academic interest only, is now of critical importance as the tumor is non-invasive and

amenable to total surgical removal. The patients usually have signs and symptoms suggestive of rheumatic heart disease with mitral valve involvement but the history and findings may also simulate embolic disease occurring in atrial fibrillation, a mural thrombus over a recent myocardial infarction, a thrombus in a left ventricular aneurysm, or cerebral thrombosis or hemorrhage.

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## HOW MUCH LIVER FUNCTION IS NEEDED FOR SHUNT?

What are your minimum criteria of liver function before you'll do a shunt?

"I would like the serum albumin to be greater than 3 grams per 100 ml, though I've done a shunt in a patient with a serum albumin at 1.8 mg and the patient did relatively well and is still alive. I don't think a marked reduction in platelet count is a deterrent since we have platelet packs available; and subsequent to the shunt, the low count reverses itself. I'd like to have the serum bilirubin below 2. . . . I'd like on a clinical basis to be able to say that the patient doesn't have any stigmata of encephalopathy.

"Probably the clinical judgment is worth far more than all the laboratory tests. I would like to give a warning about serum albumin to those of you in hospitals using the 12-channel autoanalyzer. Serum albumin determinations in this machine in those patients who are jaundiced are totally worthless and should be disregarded completely. Rely only on electrophoresis."

—Comments from a Panel Discussion titled  
"Surgical Solutions to Problems of Liver Disease."

Extracted from *Audio-Digest Surgery*, Vol. 16, No. 6, in the Audio-Digest Foundation's subscription series of tape-recorded programs.

## Mondor's Disease

H. B. WATENMAKER, M.D., *Gardena*

MONDOR'S DISEASE is a medical curiosity of uncommon occurrence and obscure cause.<sup>1</sup> Apparently it is simple thrombophlebitis of the thoraco-epigastric vein and its tributaries, occurring as a tender, cordlike structure in the area of the chest near the breast at the upper abdominal wall. Usually it is one-sided, rarely bilateral.<sup>2,3</sup> It seldom occurs in males.<sup>4</sup>

This condition was named after a French surgeon who mentioned it as a localized problem in a report in 1939, although Flagge apparently was the first to report it, in 1869.<sup>3</sup> Credit for its discovery as a clinical entity, however, should go to Fiesinger and Mathieu, who reported three cases 17 years before Mondor's report appeared, and who correctly defined the condition as we know it today.<sup>5</sup>

Despite the increased frequency of reports, few physicians are aware of this problem and Mondor's disease remains a relatively unknown condition. Since Mondor's first report, approximately 60 reports involving about 200 cases have appeared in the world literature.

Most observers apparently agree that pressure on the chest seems to trigger the inflammation of the veins.<sup>2,3,5</sup> Some have noted its occurrence following surgical operation on the breast and one investigator considered it vestigial mastitis because the lesion seemed to run along the embryonal milk ridge.<sup>3,6</sup> Still others have expressed belief it is of viral or hematological origin, although no underlying disease has been discovered. A consideration not previously emphasized in the literature is that

since the thoraco-epigastric vein serves as an important communication between the femoral and axillary veins, thrombophlebitis might develop in it by reflection from pathological changes in the lower extremities.

The involvement of this particular vein is apparently self-limiting, lasting from two to three months when the vein is canaliculated.<sup>6</sup> The patient usually complains of varying degrees of pain or soreness in the involved site, and on examination a pale pink streak may be seen on the upper abdominal wall or on the chest near the breast. On palpation along this streak a cordlike structure may be felt, and pressure usually evokes pain. Stretching the skin above or below it causes the tendinous structure to retract, the cord sinking below the level of the skin on each side of it. This retraction has been thought by some investigators to be due to malignant change, but evidence thus far has clearly not supported this supposition.<sup>5-8</sup>

There has been no specific treatment recommended for this condition, but my experience, in the case here reported, indicated spontaneous healing following biopsy of the thrombosed vein. This observation is consistent with Hedlinger's<sup>9</sup> in 1962.

### Report of a Case

The patient was a 40-year-old married Mexican-American woman with complaint of pronounced soreness, of about 2 weeks' duration, in the right lower quadrant of the chest and in the adjacent abdomen. Stretching of the skin and tissues in the area aggravated the pain, the patient said, and she could feel a lineal thickening beneath the surface. She could recall no recent trauma that might have caused this condition. A fibroma had been removed from the right breast a year previously, and 6 months before the present examination the patient had had an episode of paroxysmal tachycardia, but because of the long interval these events seemed unrelated to the current symptoms.

On examination a pale red, tender, tendinous cord 3 to 4 mm wide was felt extending from the umbilical level to the eighth right rib at approximately the anterior axillary line. This cord became quite prominent when the skin over it was stretched. No abnormality was noted in the breasts and no pathological changes in the skin, except those already mentioned.

In the 2 weeks before she sought medical attention the patient had taken aspirin and applied lini-

Submitted 30 September 1969.  
Reprint requests to: 14017 S. Van Ness Avenue, Gardena, Ca. 90249.



ment and heat to the area, all without relief or palpable change in the cord.

Proteolytic enzymes were prescribed, but after a week of no response they were discontinued. Because the patient was apprehensive about this condition, operation was done for biopsy. Under general anesthesia the cordlike lesion was dissected free of the overlying skin layers and subcutaneous tissue at its midpoint, and a one-half inch segment was excised. The cut ends were then drawn together again and ligated and the wound was closed. The pathologist's report was simply "organized thrombus of the vein involved."

A week after the operation pain had abated, and the cordlike structure was no longer visible or palpable.

### Summary

In a case of Mondor's disease of 2 weeks' duration a biopsy specimen was excised from the cord-

like structure that was visible and palpable beneath the tissues at the site of the thoraco-epigastric vein. Pain promptly abated and within a week the cord was no longer discernible by sight or touch. The pathologist reported "organized thrombus."

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### ERYTHROMYCIN AND LINCOMYCIN

What drug do you use to treat pneumococcal and streptococcal infections in patients with a clear-cut history of penicillin allergy?

"I think erythromycin has served us in very good stead. . . . In fact, it's hard to prove that penicillin is better in a given series of pneumococcal pneumonias. . . .

"Lincomycin (Lincocin®) is an isomer of erythromycin; and I can see no difference between the two, except perhaps as parenteral agents. Lincocin® is much better tolerated. It's a much better parenteral product. So if you have a penicillin-sensitive person you want to treat with a parenteral agent, I'd use Lincocin®. It works just about identically with erythromycin."

—GENE H. STOLLERMAN, M.D., Memphis  
Extracted from *Audio-Digest Internal Medicine*, Vol. 16, No. 4, in the Audio-Digest Foundation's subscription series of tape-recorded programs.

# Acalculous Cholecystitis Due to Hodgkin's Disease

EDWARD A. DAINKO, M.D., M.S.,  
*San Bernardino*

ACUTE CHOLECYSTITIS is associated with stones in the gallbladder in more than 90 percent of the cases. When stones are present, the usual cause is impaction of one of them in the cystic duct.

In the patients in whom acute cholecystitis occurs without stones in the gallbladder, the precipitating cause is usually less obvious. Obstruction of the cystic duct may be due to neighboring inflammatory reaction, fibrosis, tumor, anomalous vessels, or kinks of the cystic duct.

A case of acute acalculous cholecystitis in a 70-year-old physician with carcinoma of the cystic duct has been reported.<sup>1</sup> There have been reports also of obstruction of the common bile duct secondary to Hodgkin's tumor masses.<sup>2</sup> In a review of the literature no report could be found of acalculous cholecystitis due to Hodgkin's involvement of the cystic duct, as occurred in the following case.

## Report of a Case

The patient was a 44-year-old white man who was seen at the San Bernardino County General Hospital in early January of 1966 because of enlargement of a left cervical lymph node. Hodgkin's disease had been diagnosed in 1949 by a left supraclavicular lymph node biopsy. Local irradiation had brought about remission, the patient requiring no further treatment. In 1964 he had had myocardial infarction, and from then on had

been troubled with angina pectoris. He was treated with anticoagulants and coronary vasodilators. Further examination at that time was unremarkable. Roentgenograms of the chest revealed a widened mediastinum. Biopsy of a left cervical node revealed recurrent Hodgkin's disease. On bronchoscopy, no abnormalities were noted. The patient was discharged and shortly after returning home he began having pain in the right upper quadrant of the abdomen, associated with anorexia and nausea. The pain was steady, intense and knife-like. It was not relieved by taking Maalox®\* or Donnatal®†

On physical examination, the patient was noted to be in moderate distress. Oral temperature was 99.8° F. The pulse rate was 78 per minute. There was no jaundice. Local tenderness was present in the epigastrium and the right upper quadrant of the abdomen. All oral intake was stopped and fluids, antispasmodics and meperidine were administered intravenously.

Hemoglobin was 14 grams per 100 ml and the hematocrit was 42 percent. Leukocytes numbered 3,700 per cu mm and platelets 400,000 per cu mm. The proportion of reticulocytes was 0.8 percent. A review of previous hemograms revealed them to be essentially the same. Results of the VDRL test were negative. Urinalysis was within normal limits. An electrocardiogram was consistent with an old inferior myocardial infarction with some lateral ischemia. Roentgenograms of the chest revealed enlarged hilar lymph nodes. An upper gastrointestinal series was interpreted as normal. Attempts at oral cholecystography revealed nonvisualization of the gallbladder on two occasions, one with a double dose of dye. Liver functions and serum amylase were normal. No liver scan was obtained. The leukocyte count, determined several times, remained essentially unchanged.

Symptoms persisted and exploratory operation was done 10 January 1966. The gallbladder was noted to be thickened, erythematous and tense. An enlarged sentinel lymph node was present in Calot's triangle and a thickened, leathery, firm cystic duct was found (Figures 1 and 2). The gallbladder was removed by sharp dissection. No gallstones were present. The liver, spleen, peri-aortic lymph nodes and iliac lymph nodes were

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\*Magnesium-aluminum hydroxide.

†A compound of hyoscamine sulfate, atropine sulfate, hyoscine hydrobromide and phenobarbital (Robins).

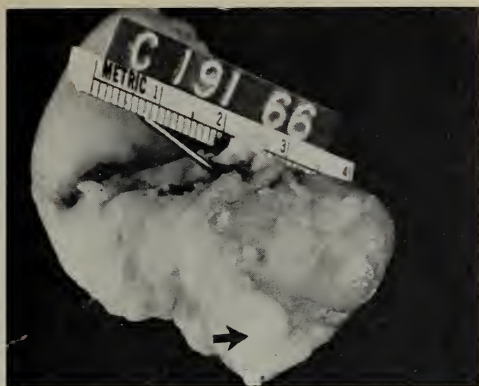


Figure 1.—Thickened cystic duct with small lumen is seen (arrow). The enlarged lymph node is seen adjacent to the cystic duct.

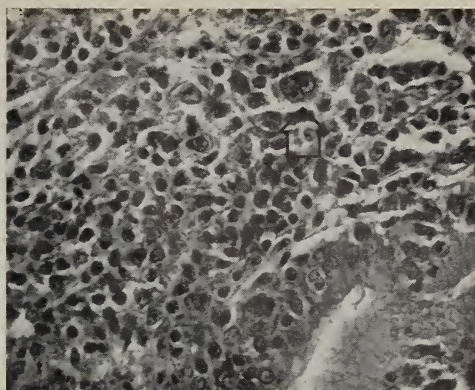


Figure 3.—The cystic duct epithelium is evident at the lower right in the illustration. Dorothy Reed-Sternberg cells are present (arrow) as well as granulocytes, fibroblasts, lymphocytes, monocytes and plasma cells. Minimal fibrosis is present. (Hematoxylin & Eosin,  $\times 570$ .)



Figure 2.—Sagittal section of the cystic duct and gallbladder shows the thickened area of the cystic duct occluding the lumen.

found to be involved with what appeared to be Hodgkin's disease.

The postoperative course was uneventful and on 3 February the patient was given an intravenous injection of nitrogen mustard, 0.4 mg per kg of body weight. This was followed by oral administration of cyclophosphamide.

Histologic examination revealed Hodgkin's disease of the gallbladder in the area of the cystic duct. Foci of infiltrations of chronic inflammatory cells were seen in the fundus of the gallbladder. Multinucleated Dorothy Reed-Sternberg cells were frequent (Figure 3).

The patient is observed regularly in the outpatient department. Hydralazine (Apresoline®)

and reserpine are given for hypertension. He has had several courses of intravenous nitrogen mustard and is currently receiving cyclophosphamide by mouth. When last seen, in September of 1969, he was doing well.

## Discussion

Progressive cholecystitis usually is manifested by rising fever and pulse rate, increasing right upper quadrant abdominal pain and increasing leukocytosis. It usually follows impaction of a gallstone in the cystic duct. As the gallbladder distends, it becomes more inflamed and perforation may occur.

The clinical symptoms in the present case differed in that the usual signs of acute inflammation were absent, there was no significant rise in temperature or pulse rate, and leukocyte count remained essentially unchanged. However, the right upper quadrant abdominal pain remained localized and did not improve.

Primary or secondary lesions of Hodgkin's disease may arise anywhere along the gastrointestinal tract. However, the lesions most often occur in the stomach and small bowel. There has been no previous recorded case of Hodgkin's disease of the cystic duct causing cholecystitis. Most of the lesions of the alimentary tract are associated with a generalized disease. In the more advanced cases of Hodgkin's disease, some involvement of the liver is quite common. This may be evaluated by liver scanning techniques. Jaundice and ascites



may accompany the hepatic enlargement. Whether jaundice is to be explained by the assumption of deposit of the disease at the portal area or intrahepatic biliary tract obstruction, or hepatocellular disease of viral causation, may be an intriguing diagnostic problem. The results of liver function tests may be equivocal. In a study by Levitan, Diamond and Craver<sup>3</sup> the liver was noted to be the seat of some lesion in two-thirds of 112 cases of Hodgkin's disease that came to postmortem examination. Diffuse infiltration was the most common type of lesion. The symptoms of obstructive jaundice seem to result more frequently from intrahepatic biliary obstruction than from pressure or invasion of the portal outlet.<sup>2</sup> The differentiation of cause of jaundice is obviously of importance to the decision about modes of therapy.

Three histologic gradings of Hodgkin's disease proposed by Jackson and Parker<sup>4</sup> are termed *paragranuloma*, *granuloma* and *sarcoma*. The *paragranuloma* is characteristically predominantly composed of adult lymphocytes. Careful search is often required to find the Reed-Sternberg cells. When Reed-Sternberg cells are mostly mononuclear without globing, being presumably early forms, the distinction between *paragranuloma* and lymphocytic lymphosarcoma may be difficult. *Paragranuloma*, or even *granuloma*, may also in some cases be read into biopsy slides that other pathologists would interpret as showing chronic lymphadenitis. This distinction is naturally of paramount importance to the clinician; but in some cases, further lapses of time and study of further biopsy material may be the only means of enabling a clear-cut decision.

Hodgkin's granuloma, while usually showing the characteristic cellular complex, nevertheless is sometimes difficult to distinguish from other granulomatous or other changes in lymph node structure. Examples of other processes whose histologic features may, on occasion, be mistaken for those of Hodgkin's granuloma are many. In the Hodgkin's granuloma, the nuclei of the Reed-Sternberg cells are mostly multilobed or, less often, multiple with prominent nuclei. Histologically characteristic of Hodgkin's granuloma is a mixture of granulocytes, fibroblasts, lymphocytes, plasma cells, monocytes and histiocytes, often with areas of necrosis and at times more or less extensive fields of fibrosis. But, in all this variety, the one essential diagnostic criterion is the Reed-Sternberg cell.

### Summary

Acute cholecystitis is most often associated with gallbladder calculi obstructing the cystic duct. A case of Hodgkin's disease involving the cystic duct of the gallbladder causing obstruction is presented and discussed. The absence of most of the usual signs of acute cholecystitis in the case reported is noted.

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### OCCUPATIONAL THERAPISTS USED IN "EYE TRAINING"

"As an ophthalmologist, I've found I get the greatest amount of help in treating patients with low vision by calling in the occupational therapist. Giving a person a device to improve his vision and saying, 'Here, go home and use it,' is like going into some of our slum areas and saying, 'Here's \$10,000,000; make a man of yourself.' Another step is needed; and for that I use the occupational therapy department. Patients think they are going for exercises, but they are really going to be oriented. They're given a task to do; they use their devices; they become familiar with them; and then they take them home and use them."

—ALBERT E. SLOANE, M.D., Boston

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# Local and Systemic Factors in the Pathogenesis of Thrombosis

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THE PURPOSE OF THIS REPORT is to develop a formulation of the pathogenesis of thrombosis in which three entities are separated from each other—the arterial thrombus, the red (stasis) thrombus, and the syndrome of disseminated intravascular coagulation. Each of these forms of thrombosis has distinct pathophysiologic features, arising from distortions of different segments of the normal hemostatic sequence. In each there is a different balance between local and systemic factors predisposing to vascular occlusion, and in each there is a characteristic response to anticoagulant therapy.

Clarification of the pathogenesis of thrombosis has emerged from a rapid expansion of knowledge of the normal hemostatic process. During the past decade, as a result of detailed electronmicroscopic studies of hemostatic plug formation, and as a consequence of entirely new concepts of platelet aggregation mechanisms, there has been a shift in the theory of the hemostatic process.<sup>1,2</sup> Previously, most investigators believed that the hemostatic mechanism was in continuous operation; that there was continued deposition of fibrin on normal vessel walls, thereby maintaining vascular structural in-

tegrity; and that the rapid turnover of most coagulation factors reflected the consumption of clotting proteins during this continuous process. As Hjort<sup>2</sup> has emphasized, the central assumption of this viewpoint was that the hemostatic mechanism presumably acted at all times upon normal, uninjured endothelium, and that local tissue injury served merely to accelerate an otherwise slowly operative process. It is now recognized, however, that the normal hemostatic process is in fact not continuously operative. Rather, it is essentially an intermittent process, activated only in response to local injury. Accumulated evidence discounts the concept that the turnover of clotting factors reflects their utilization during normal hemostasis. The fundamental new concept is that the hemostatic process is not operative on normal endothelium, but requires a "structural trigger"<sup>3</sup> to initiate hemostasis. That trigger is injury to the vascular endothelium.

## The Normal Hemostatic Mechanism

The normal hemostatic process begins when a blood vessel is injured and culminates in the formation of a fibrin-platelet meshwork that is a structural barrier to the escape of blood at the site of injury.<sup>4</sup> The most immediate and direct response to injury is vascular constriction.<sup>5-8</sup> The hemostatic significance of vascular constriction is

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intuitively apparent, for if a vascular bed that cannot constrict is transected (for example, the telangiectatic vessels in Osler-Weber-Rendu disease) prolonged and profuse bleeding results even if all other components of the hemostatic mechanism are intact. Although a few studies of this most fundamental response to injury have been made, the mechanisms whereby vessel injury provokes vasoconstriction are largely uncharacterized.

The trigger that initiates subsequent hemostatic reactions is the separation or disruption of the endothelium, thereby allowing flowing blood to contact subendothelial connective tissue. At once, the platelets immediately adjacent to the site of injury adhere to the connective tissue, and, rapidly, additional platelets brought to the site of injury by the flowing blood form large aggregates which extend from the site of injury into the blood vessel lumen, forming the initial or temporary hemostatic plug.

New knowledge of the mechanisms by which the temporary hemostatic plug is formed represents a major advance in our understanding of hemostasis and has greatly clarified our concepts of the pathogenesis of thrombosis. That collagen was the specific component of connective tissue to which platelets adhere was first suggested by Hugues<sup>9-11</sup> and by Bounameaux.<sup>12</sup> This proposition was repeatedly confirmed in other laboratories.<sup>13-15</sup> It is now established that the adherence of platelets to collagen is independent of ionized calcium,<sup>13,16</sup> that no plasma cofactors are required,<sup>13,16</sup> that the maintenance of the native triple helical structure of collagen is essential,<sup>17</sup> but that removal of negatively charged telopeptides by pepsin does not affect platelet adherence.<sup>17,18</sup> Furthermore, blockage of free amino groups of lysine profoundly diminishes the reactivity of collagen with platelets, whereas acetylation of the carboxyl groups of collagen does not interfere with platelet adherence.<sup>17</sup>

The stimulus that leads to the piling up of aggregated masses of platelets extending away from the site of injury into the vascular lumen has also been clarified. The essential mediator of this process is the nucleotide adenosine diphosphate (ADP). That ADP could aggregate platelets was first established by Hellem<sup>19</sup> and by Gaarder<sup>20</sup> and her associates. Subsequent studies have shown that as platelets adhere to collagen,<sup>16,21,22</sup> they release ADP; that the amount of

ADP released is sufficient to cause further aggregation of platelets<sup>23</sup>; and that the aggregation of platelets caused by epinephrine<sup>24</sup> and thrombin<sup>25</sup> is also ADP-mediated. When radioactive phosphate or adenosine are incubated with platelets, they are incorporated into platelet nucleotides, including ADP. When such labelled platelets are aggregated by collagen or by thrombin, release of ADP is readily detectable by chemical assays, but no radioactive nucleotides are released.<sup>22,26</sup> These studies indicate that two pools of ADP exist in the platelet and that release of ADP occurs from only one of them. In contrast to the collagen-initiated reaction, ADP-induced platelet aggregation occurs only in the presence of divalent cations,<sup>27-29</sup> and requires fibrinogen and a heat-stable plasma protein for maximal aggregation to occur.<sup>30-33</sup>

Recently, several drugs have been found which can selectively interfere with the sequence involved in platelet aggregation. Thus, aspirin<sup>34,37</sup> and the pyrazole<sup>38</sup> compounds such as phenylbutazone block the release of ADP by collagen, epinephrine, and by ADP itself. Furthermore, the vasodilator dipyridamole directly inhibits the aggregation reaction caused by ADP.<sup>24</sup> In addition familial disorders<sup>39-43</sup> have been described in which the platelet release of ADP in response to aggregating reagents is impaired as a hereditary defect. Thus, the selective defects either inherited or induced by drugs emphasize the sequence of the initial reaction in the hemostatic process.

The ultrastructural changes that accompany platelet aggregation reactions have been extensively studied.<sup>44-49</sup> Platelets circulate normally as ovoid discs. Immediately underneath their plasma membrane, platelets contain a marginal band of microtubules which appear to be under some degree of centrifugal tension. It has been postulated that this marginal band of microtubules maintains the disc-like shape of the platelets. Platelets also contain mitochondria, lysosomal granules, and glycogen. When platelets contact collagen, striking changes occur. The platelets swell, the marginal band of tubules is disrupted, and the lysosomal granules and mitochondria disintegrate. In contrast, when the platelets aggregate in response to ADP, they swell, but the marginal band of microtubules is now found in the interior of the cell where it tightly surrounds intact, closely approximated lysosomal granules and mitochondria.



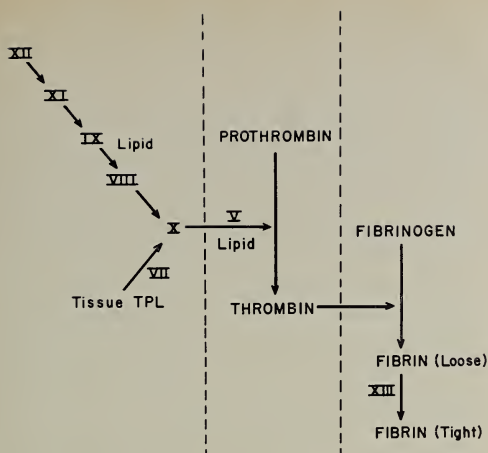


Chart 1.—The Clotting Sequence. Nomenclature: Factor XII=Hageman; Factor XI=Plasma Thromboplastin Antecedant (PTA); Factor IX=Plasma Thromboplastin Component (PTC, Christmas Factor); Factor VIII=Antihemophilic Factor (AHF); Factor X=Stuart Factor; Factor VII=Serum Prothrombin Conversion Accelerator (SPCA); Factor II=Prothrombin; Factor V=Proaccelerin; Factor I=Fibrinogen; Factor XIII=Fibrin Stabilizing Factor.

NOTE: All steps subsequent to the activation of XI by XII require ionized calcium.

The subsequent steps in the hemostatic process involve the transformation of the temporary hemostatic plug, formed by the loose platelet aggregates, into a permanent plug stabilized by fibrin. This transformation is brought about by activation of the blood clotting mechanism. The critical steps in this sequence are the conversion of prothrombin to thrombin and the subsequent conversion of the soluble protein fibrinogen to an insoluble polymer of fibrin.

There are two major pathways by which prothrombin is converted to thrombin. The first of these, the so-called "intrinsic pathway," is initiated by the conversion of Hageman factor or factor XII from an inert precursor to an activated form.<sup>50</sup> *In vitro*, substances that have electronegatively charged, wettable surfaces are capable of transforming the Hageman factor.<sup>51,52</sup> Such surfaces include glass and collagen fibers.<sup>53</sup> It is probable that in the injured vessel, exposure of collagen to the plasma proteins is the initial step in the activation of the intrinsic pathway. Recent studies have shown that the presence of free carboxyl groups is essential for collagen-induced transformation of Hageman factor.<sup>53</sup>

Once factor XII is activated, it initiates a series of reactions that have been described as a waterfall<sup>54</sup> or cascade<sup>55</sup> in which certain blood clotting factors are sequentially converted from their inactive or precursor form to their active or enzymatic form (Chart 1). Thus, activated factor XII activates factor XI (PTA), which in turn activates factor IX (PTC or the Christmas factor). The reaction between activated factor IX, factor VIII (the anti-hemophilic factor) and factor X (Stuart factor) is a complex one. It is not yet certain whether factor IX activates factor VIII, which in turn activates factor X, or whether activated factors IX, VIII and platelet lipids together form a complex which activates factor X. Activated factor X in the presence of coagulation factor V and phospholipid (derived from platelets) converts prothrombin to thrombin. Thrombin then converts fibrinogen to fibrin monomer, which spontaneously polymerizes. However, this polymer is a loose and easily dissociated aggregate held together only by hydrogen bonding. Yet another clotting factor, factor XIII<sup>56</sup> or the fibrin stabilizing factor, converts the hydrogen bonds to covalent links, forming the dense, tight fibrin that is the final product of the coagulation sequence.

The "extrinsic pathway" is a second mechanism which activates prothrombin. Many tissues, particularly blood vessel walls, lung and brain, contain a microsomal lipid-protein complex called tissue thromboplastin which is directly capable of activating factor X in the presence of an accessory cofactor, factor VII.<sup>57,58</sup> Activated factor X then reacts in an identical fashion to that already described and converts prothrombin to thrombin. In this pathway, however, the lipid required for the conversion of prothrombin is derived from the tissue thromboplastin itself and platelet lipids are not required.

As a result of the activation of both pathways of the clotting mechanism, thrombin is produced explosively at the site of tissue injury. If unchecked, the local production of thrombin could theoretically lead to massive systemic defibrination, for there exists in 15 ml of blood sufficient potential thrombin (if prothrombin were completely converted to thrombin) to clot 2,500 ml of plasma in 15 seconds. Clearly, there are efficient mechanisms which limit the hemostatic process and confine it to the site of local injury. Several kinds of limiting reactions are operative: those that re-

tard the formation of thrombin; those that block the reaction of thrombin and fibrinogen; those that affect the conversion of fibrinogen to fibrin; and the effects of rapid blood flow.

There is in blood a series of inactivators which progressively impede the procoagulant activity of each of the precursors of prothrombin.<sup>59-61</sup> Thus, when shed blood clots in siliconized test tubes *in vitro*, certain of the thrombin precursors disappear from the resulting serum. Although the levels of factors XII, XI, IX and X remain relatively unaltered, factor VIII and factor V activity in serum is greatly depressed. However, if shed blood is clotted in the presence of potent activators of the contact system, the content of factors IX, X, and XI in the serum is greatly reduced. Finally, if shed blood is clotted in the presence of tissue thromboplastin, the resulting serum contains little factor X activity, but the levels of factors XII, XI, and IX are unaltered. These observations may be rationalized by the concept that the disappearance of clotting factor activity in shed blood reflects the selective inactivation of the activated, rather than the inert or precursor form of the procoagulants. Under conditions which favor maximal activation of a procoagulant, its activity will be selectively depressed in serum. However, since the inactivation of factors V and VIII is primarily influenced by the presence of thrombin, depression of these two factors will be present in all circumstances in which shed blood is allowed to clot. The blood inactivators of thrombin precursors share another property: the rate of inactivation of an activated clotting intermediate is relatively slow. In recent experiments we demonstrated that the apparent *in vitro* half-time of decay of activated factor X in serum exceeded 50 minutes.<sup>62</sup>

In addition to the blood inhibitors, there are efficient tissue mechanisms that also participate in the removal of activated clotting factors. The clearance of activated procoagulants from the circulation was first demonstrated by Spaet and Kropatkin<sup>63</sup> in 1958. They demonstrated that intravenously injected soluble blood thromboplastin precursors were ineffective in producing the defibrination syndrome, and they suggested that a cellular clearance mechanism might be operative in the removal of activated procoagulants. In subsequent studies Spaet and his associates demonstrated that the reticuloendothelial system removes particulate blood thromboplastin, and that

liver removes activated factor X formed by the operation of the intrinsic coagulation mechanism.<sup>64</sup> In other studies from our laboratory we have also demonstrated that factor X, activated either by trypsin or by Russell's viper venom, was removed by the liver with an apparent half-time of approximately seven minutes.<sup>62</sup> The mechanism of hepatic cellular clearance of activated procoagulants has not been established. It has been demonstrated that there is no release of an hepatic inhibitor,<sup>64,65</sup> but whether the attenuation of activated factor IX or X activity that can be demonstrated upon perfusion of these activated precursors through isolated liver preparations represents interhepatic degradation of procoagulants or interhepatic binding of the procoagulants is not yet clear.

In our experiments,<sup>65</sup> intense activation of the intrinsic system *in vivo* was produced by the infusion of thrombin-free serum into rabbits. In these experiments infusion of serum directly into the portal vein was far less effective in producing systemic hypercoagulability than was infusion of serum into a peripheral vein. Furthermore, when serum was infused into animals in which the hepatic circulation was occluded, widespread thrombosis occurred in all major vascular systems. These studies demonstrated that the liver played a key role in the attenuation of the hypercoagulable response to serum. These observations have been extended by the finding that during liver transplantation, striking acceleration of intravascular coagulation becomes apparent when the liver is removed from the circulation.<sup>66</sup>

The inactivation of clotting factors has been demonstrated primarily in shed blood. During normal hemostasis, the levels of circulating procoagulants remains unaltered. Conversely, the role of the hepatic clearance mechanism has been demonstrated in experiments in which there has been systemic rather than local stimulation of the coagulation mechanism. Therefore, the relative role of these two mechanisms in limiting the growth of the normal hemostatic plug has not yet been established.

When thrombin is added to plasma, it is rapidly neutralized. As many as six different antithrombic activities (each with a different Roman numeral) have been described. However, it is now clear that there are only two major mechanisms by which thrombin is neutralized during the normal hemostatic process. The first of these is the physical



removal of thrombin from the solution by adsorption to fibrin.<sup>67</sup> It has been demonstrated that fibrin rapidly binds a large excess of thrombin and that this adsorption accounts for the major portion of the rapid disappearance of thrombin when it is added to plasma. The adsorptive capacity of fibrin for thrombin has been given the term antithrombin I.

Another mechanism is also operative, for thrombin is also neutralized when it is added to defibrinogenated blood or to serum. In contrast to the immediate removal of thrombin by adsorption to fibrin, the neutralization of thrombin in defibrinogenated plasma is a time-consuming process. The activity responsible for the progressive inactivation of thrombin in serum or plasma has been termed antithrombin III.<sup>68</sup> It has been recently demonstrated that progressive antithrombin directly interferes with the ability of thrombin to release fibrinopeptides from fibrinogen.<sup>69</sup> Antithrombin does not influence the subsequent polymerization of fibrin monomer. In addition, the same protein that is responsible for the progressive inactivation of thrombin also appears to be identical with the cofactor required for the antithrombotic action of heparin (previously termed antithrombin II).

The relative importance of thrombin adsorption and thrombin inactivation in the normal hemostatic process has not been established. At least one investigator<sup>70</sup> believes that adsorption represents the only significant physiologic process, but others<sup>71,72</sup> feel that both adsorption and inactivation are physiologically operative. One observation that emphasizes the importance of progressive antithrombin is a description of a kindred with a defective progressive antithrombin activity.<sup>73</sup> In this family there was a high incidence of thromboembolic disorders.

The fibrinolytic system plays a major role in the maintenance of the fluidity of the blood, particularly in the small vessels. Vascular endothelium contains a potent tissue activator which converts an inert protein plasminogen into the potent enzyme plasmin. Unlike thrombin, plasmin is rather non-specific. It digests factors V, VIII, fibrin, fibrinogen itself, and certain of the components of complement.<sup>74</sup> The tissue activators of plasminogen are released from blood vessel walls by injury or by anoxia.<sup>75</sup> Furthermore, activated factor XII and thrombin itself can also convert plasminogen to plasmin.<sup>76</sup> Thus, activation of the

fibrinolytic mechanism inevitably is linked to the activation of the hemostatic process and must be considered an integral component of hemostasis. It has been shown that there is an inverse relationship between vessel size and fibrinolytic activity.<sup>77</sup> Recent studies have demonstrated the resistance of small vessels to occlusive thrombus formation.<sup>78</sup> When systemic hypercoagulability was produced in rats by the infusion of serum, occlusive thrombi formed in isolated large vein segments. No thrombus formation was observed, however, in veins with a diameter of less than 50 microns. Pretreatment of rats with epsilon-amino caproic acid before the infusion of serum resulted in fibrin deposition in all the small veins and enhanced thrombus formation in the larger vessels as well. These observations emphasize the function of the fibrinolytic system in preventing occlusive thrombus formation in small vessels.

The mechanism by which activation of plasminogen maintains the fluidity of blood in small vessels may be largely a reflection of the elaboration of inhibitors of fibrin polymerization and of the thrombin-fibrinogen reaction.<sup>79,80</sup> When plasmin reacts with fibrinogen, a sequential degradation of the fibrinogen molecule occurs. If the reaction is allowed to proceed to completion *in vitro*, three classes of fragments are produced: one with a molecular weight of approximately 88,000; a second with a molecular weight of approximately 30,000; and a third heterogeneous group of fragments of lower molecular weight. Although these fragments are not clottable by thrombin (and thus persist in serum) they exert a powerful inhibitory effect on the polymerization of fibrin monomer. They not only retard the rate of fibrin monomer polymerization, but they also become incorporated into the growing fibrin polymer producing a defective, fragile fibrin mesh with a highly abnormal structure. In addition early in the reaction between plasmin and fibrinogen large abnormal fibrinogen fragments are produced. These fragments also are potent anticoagulants. They exert their effect both on the polymerization of fibrin monomer and on the conversion of fibrinogen to fibrin monomer. On a molar weight basis, these early fibrinogen-derived fragments are much more potent than are the late products of plasmin digestion of fibrinogen. Unlike the end products of plasmin-fibrinogen interaction, the early fragments are partially clottable by thrombin, though at a retarded rate. Thus, they are not present in serum.



There are other mechanisms by which activation of the fibrinolytic mechanism may retard thrombus formation. Thus, it has been observed that fibrinogen degradation products interfere with platelet aggregation reactions, and it is known that plasmin degrades factors V, VIII and IX as well as fibrinogen.<sup>74</sup> Whether or not these ancillary effects of plasmin play a significant role in the limiting of the normal hemostatic process has not yet been established.

In addition to those factors already described, the complex effects of blood flow on limiting spread of the hemostatic plug must be considered. Rapid blood flow serves two functions: it dilutes the local concentration of activated blood clotting factors, and it mechanically opposes the spread of the growing platelet mass.

As in the elucidation of the components of the clotting sequence, the participation of each mechanism in the limitation of the unchecked spread of the hemostatic plug is more easily recognized by its absence than by its presence. Thus, the role of the liver in clearing activated coagulation factors is emphasized by the acceleration of intravascular coagulation that occurs when the hepatic circulation is occluded. The role of antithrombin is accentuated by the high incidence of thromboembolic disease in its absence. The normal protective role of the fibrinolytic system is uncovered when inhibitors of fibrinolysis are employed. Finally, the importance of rapid blood flow is emphasized by the importance of vascular stasis in the etiologic derivation of clinical intravascular thrombosis — an observation that has been entrenched since the time of Virchow.

From the foregoing discussions we may now summarize the events that occur in the normal hemostatic response. First, the blood vessel contracts in response to vessel injury. In addition, as the endothelial barrier is broken, subendothelial collagen is exposed to the blood vessel lumen. This exposure to collagen initiates a series of platelet reactions mediated at first by collagen itself and subsequently by adenosine diphosphate, producing an occlusive plug of platelets that extends from the site of vascular injury into the lumen of the contracted blood vessel where it provides the first or temporary barrier to blood loss. Simultaneously, the exposure of collagen to plasma and the release of tissue thromboplastin activate both the intrinsic and extrinsic systems of blood coagulation, result-

ing in the explosive production of thrombin at the site of vascular injury. In the presence of thrombin the platelet plug undergoes transformation and becomes a non-reversible mass intertwined with fibrin. The process of hemostatic plug formation is limited by a series of complex reactions which include adsorption of thrombin, inhibition of precursors of thrombin and of thrombin itself, hepatic cellular clearance mechanisms, fibrinolytic activation, and rapid blood flow. As a consequence of the balance between hemostatic plug formation and limiting reactions, the circulation is occluded only locally in areas of tissue damage. Tissue ischemia does not ensue, and there are no distant sequelae.

### Red (Stasis) Thrombus Formation

Thrombosis cannot readily be defined as a single pathologic entity. To do so results in a viewpoint that rejects all morphologic variants of thrombi that differ from the classic mixed arterial lesion as curiosities and artifacts. Rather, a concept of the pathogenesis of thrombosis more in keeping with our present understanding of the hemostatic sequence recognizes at least three forms of thrombus — the white or arterial thrombus, the red or stasis thrombus, and the syndrome of disseminated intravascular coagulation. The pathophysiologic lineage of each of these processes is determined both by the interplay of local and systemic factors in the *initiation* of the thrombus and by the role of blood flow in the *propagation* of the thrombus. The validity of this distinction is further buttressed by the response of each of these forms to anticoagulant therapy.

Morphologically the thrombus that forms in columns of static blood closely resembles a blood clot formed *in vitro* in a glass tube. It consists primarily of a meshwork of fibrin strands in which the formed elements of the blood are trapped in a random fashion. It is found primarily in the venous tree, or, when found on the arterial side of the circulation, it exists as the propagating red tail distal to an occlusive white thrombus. Unlike the events in the formation of the hemostatic plug, no clear "structural trigger" can be defined which precipitates venous thrombosis. Clearly, in most instances of thrombophlebitis morphologic disruption of the endothelium cannot be identified. Furthermore, in certain clinical settings, for example, malignant lesions of the lung and gastrointestinal tract, the occurrence of multiple episodes of

spontaneous venous occlusion widely separated throughout the venous tree suggests that a systemic stimulus may be capable of initiating venous thrombosis in areas of retarded blood flow. The concept of a systemic "trigger" for thrombosis has derived strong experimental support from laboratory models which have demonstrated that activation of the intrinsic system *in vivo* results in the deposition of red thrombi in areas of stasis.<sup>67,81-83</sup> At the moment there is no clear idea of what the stimuli are that spontaneously activate the intrinsic mechanism in those states that predispose to venous thrombosis. It is not known, for example, whether they arise in the general circulation or locally in areas that are predisposed to thrombosis. It is known, however, that stasis is necessary for the red thrombus to form. Stasis provides two functions: it prevents dilution of activated blood-coagulation factors by blood flow, and it prevents the clearance of activated blood-coagulation factors by the hepatic clearance mechanism. What, then, can one say about the balance between local and systemic factors in the development of venous or stasis thrombus? From clinical and experimental observations it seems likely that at least in some large fraction of spontaneous venous thrombosis a systemic stimulus acts as the trigger. Clearly, however, local stasis determines at which point the venous thrombi form. Thus, activation of the blood clotting system and local stasis together participate in the pathogenesis of the red thrombus.

### White (Platelet) Thrombus Formation

The thrombus that forms on the arterial side of the circulation is composed primarily of platelets and fibrin, called by pathologists the white thrombus. It forms almost exclusively in areas of rapid blood flow in association with an injured or abnormal vessel wall, generated in most instances by an atheromatous plaque but in others from other lesions that interrupt the normal endothelial barrier. Although earlier investigators held that intimal injury produced damaged endothelial cells to which platelets adhered, Spaet<sup>3</sup> and French<sup>84</sup> have marshalled impressive evidence that in fact the initiating event in the formation of arterial thrombosis is the denudation of the endothelium and exposure of platelets to subendothelial collagen. Therefore, the "structural trigger" in the formation of arterial thrombosis resembles that in the initiation of the hemostatic plug. It is mediated primarily by plate-

let reactions with collagen and does not depend primarily on the blood coagulation system.

In contrast to the events in the small vessel the platelet mass is initially non-occlusive since it does not form in a constricted vessel. It grows continuously as the blood stream brings to it a new supply of platelets. Counterbalancing the accretion force, however, is the disruptive force of the axial flow of the blood stream, which sweeps away the most peripheral parts of the newly forming thrombus. Thus, the white thrombus initially tends to be mural in configuration. As the mural thrombus continues to grow, perhaps in association with extension or expansion of the underlying atherosclerotic lesion, circulation in the immediate area slows. In the presence of the locally activated blood-clotting system, areas of stasis or red-thrombus accretion may become intermeshed with a white platelet nidus. These areas then become coated with new platelets from the ambient blood, forming the white lines of Zahn. Finally, as the circulation is completely occluded, thrombus formation proceeds entirely through the red-thrombus mechanism. This sequence then leads to the evolution of the mixed thrombus, the most frequently observed gross pathologic lesion on the arterial side of the circulation. One need not invoke any systemic factors in the production of the arterial thrombus, and, indeed, there is little evidence to suggest that any systemic activation of the blood coagulation system is *primarily* operative in the formation of the arterial thrombus. Thus, the arterial thrombus like the hemostatic plug remains primarily a locally determined phenomenon.

### Disseminated Intravascular Coagulation

A third form of thrombosis is the deposition of fibrin in the microvasculature throughout the body, particularly in the liver, kidney, spleen and brain. In man such diffuse deposition of fibrin throughout the body is seen in diverse syndromes including amniotic fluid embolism following incompatible blood transfusion reactions, during the course of malaria, in the retained dead fetus syndrome, in association with malignant disease of either the solid organs or of the blood-forming system, and in Gram-positive septicemia. This generalized and widespread thrombosis is given the descriptive term of disseminated intravascular coagulation. This syndrome was discussed in detail by McKay<sup>85</sup>



in a recent review article in *CALIFORNIA MEDICINE*. Briefly, it is the result of the release of pre-coagulant materials into the blood stream. For example, in the retained dead fetus syndrome and in amniotic fluid embolism, thromboplastin is released into the blood stream, thereby activating the extrinsic coagulation system throughout the body. In other syndromes procoagulant material is released which activates the intrinsic system. Whatever the stimulus, as a result of progressive coagulation within the flowing blood stream itself there is marked consumption of certain of the blood clotting factors and in addition there is often activation of the fibrinolytic mechanism. As a result of this complex interaction the whole hemostatic mechanism crumbles and the patient often presents with symptoms of diffuse intravascular occlusion and simultaneously of a widespread bleeding disorder. Whether or not actual fibrin deposition occurs in small vessels reflects a balance between the intensity of the stimulus, the efficiency of hepatic clearance mechanisms, and the degree of activation of the fibrinolytic system. Therefore, in this syndrome the accumulation of fibrin deposits when they occur in the microvasculature is a purely passive phenomenon that reflects a systemic disease process in which local factors are not primarily operative. In this instance the stimulating factor is systemic; it is mediated by the blood clotting system; and it is always a hallmark of some other concomitant disease process.

### Anticoagulant Therapy

The response to anticoagulant therapy of each form of thrombosis reflects both the mode of action of anticoagulant drugs and the primary pathologic stimulus to the formation of the thrombus. Direct anticoagulants, such as heparin, block the activation of factor IX and prevent the reaction between

thrombin and fibrinogen. The coumarin agents retard the synthesis of factors IX, II, VII, and X. Therefore, the commonly employed anticoagulant agents derive their benefit exclusively from their action on the coagulation mechanism. It has been repeatedly demonstrated that these agents in clinically safe doses have no effect on platelet aggregation reactions and do not block the initial events in the hemostatic sequence — that is, the reactions between platelets and collagen and the aggregation of platelets in response to adenosine phosphate. Furthermore, anticoagulants have no effect on the formation and development of the atherosclerotic plaque.

From these considerations it is clear that anticoagulants cannot be expected to have a significant beneficial role in the prevention of the formation or extension of the white or arterial thrombus. Indeed, critical review of often contradictory literature leads inevitably to the conclusion that there is little to support the concept that anticoagulant agents have had, in fact, a demonstrated therapeutic role in the treatment of the arterial lesion.<sup>86,87</sup> In contrast, there is little doubt that anticoagulation therapy has had a decidedly beneficial role in the prophylaxis and treatment of the red venous thrombus. Controlled studies have demonstrated the efficacy of anticoagulant agents in the treatment of recurrent pulmonary embolism<sup>88</sup> and in the prevention of pulmonary embolic disease in settings in which a high incidence of recurrent venous thrombosis may be expected.<sup>89,90</sup> In addition, in those studies which showed little benefit of anticoagulant therapy in reducing recurring white thrombus formation, there was a striking reduction of venous thrombosis in almost all such studies.<sup>86</sup> Conversely, since the red thrombus originates primarily from an abnormality in the coagulation mechanism it is not surprising that dipyrimidole, which affects

TABLE 1.—*Pathogenesis of Thrombosis*

Type of Thrombus	Pathogenesis	Response to Anticoagulant Therapy
White Thrombus	Platelet reactions with abnormal vascular wall, in areas of rapid flow. Local factors predominate	No significant response to conventional anticoagulant therapy. Efficacy of anti-platelet agents not yet established.
Red Thrombus	Activated coagulation mechanism in areas of retarded flow. Local factors (stasis) and systemic factors (activating stimulus) operative.	Beneficial response to heparin and coumarins established.
Disseminated Intravascular Coagulation	Diffuse activation of coagulation and fibrinolytic mechanisms. Systemic factors predominate.	May be reversed by heparin.



platelet aggregation reactions, should have no effect in reducing the incidence of clinically detectable deep vein thrombosis.<sup>91</sup> Finally, there is convincing evidence that heparin is the drug of choice in the disseminated intravascular coagulation syndrome. Several studies have shown that there is prompt restitution of fibrinogen to normal levels with return of the platelet count to normal and cessation of bleeding when heparin is given in the course of disseminated intravascular coagulation.<sup>92,93</sup> It is of interest that in the therapy of this disease process which reflects an intense activation of the entire coagulation syndrome, the coumarin agents have been shown to be less effective than heparin.<sup>93</sup> These observations — ineffectiveness of anticoagulants in the prevention of the white thrombus, the efficacy of both coumarin agents and heparin in the prevention of the red thrombus, and the selective efficacy of heparin in the treatment of the disseminated intravascular coagulation syndrome — emphasize once again the differing pathophysiologic lineage of each of these forms of thrombosis (Table 1).

## Summary

In summary, this report has considered in detail the normal hemostatic mechanism as a balanced concert of forces that leads to local hemostasis without tissue ischemia. Three forms of thrombosis have been presented, each postulated to arise from a different abnormality within the hemostatic system. Each represents a different balance between systemic and local factors and each has a characteristic response to anticoagulant therapy. The white thrombus arises primarily as an abnormality of the interaction between circulating platelets and an abnormal vessel wall. It is found primarily on the arterial side of the circulation and represents a purely local disorder. Anticoagulant therapy has not been shown to be of benefit in prophylaxis of this disorder. The red thrombus, which is primarily a red cell and fibrin mass, is found exclusively in areas of retarded blood flow, usually adjacent to normal blood vessel walls. The red thrombus represents a combination of a systemic process, activation of the intrinsic coagulation mechanism, and a local process, stasis. Insofar as the red thrombus is mediated by the coagulation process, anticoagulant therapy has been shown to be of benefit. Finally, disseminated intravascular coagulation, the deposition of fibrin in small vessels

throughout the body, is a consequence of coexisting disease and a systemic activation of the coagulation system. In this syndrome the local manifestations are exclusively secondary to the other disease processes. Heparin is the drug of choice in the treatment of this disorder. The differing response of each form of thrombosis to anticoagulant therapy emphasizes the varying pathophysiology of each form of thrombosis.

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# Specialty Conferences

## Carotid Sinus Nerve Stimulation in the Treatment of Angina Pectoris and Supraventricular Tachycardia

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DR. E. BRAUNWALD:\* The carotid sinus is a dilatation of the internal carotid artery near its origin at the bifurcation of the common carotid artery. This area of the vessel is richly supplied by nerve receptors which lead into the carotid sinus nerve; the latter in turn joins the ninth cranial nerve, the glossopharyngeal, which leads to vasomotor centers in the medulla. Since the classic work of Hering in 1923 it has been known that the carotid sinuses play a critical role in the regulation of arterial pressure. Stimulation of the pressure receptors (baroreceptors) in the carotid sinuses and aortic arch results in reflex arteriolar dilation and reduction of heart rate and myocardial contractil-

ity, this as a consequence of a reduction in the frequency of sympathetic efferent impulses and an increase in the frequency of vagal impulses.<sup>1</sup> The opposite changes occur when the pressure acting upon these receptors is reduced. For this reason, the sensory nerves from the baroreceptors are called buffer nerves; in normal circumstances they are continuously active in the regulation of arterial pressure, heart rate and myocardial contractility.

It is well known that profound circulatory changes can be induced by carotid sinus nerve stimulation. For many years manual stimulation of the carotid sinuses has been commonly used for interrupting supraventricular tachycardia. More recently, Schwartz<sup>2,3</sup> and his associates as well as other investigators<sup>4,7</sup> have implanted electrodes on the carotid sinus nerves of patients with hypertension which was unresponsive to conventional treatment, and by stimulating the nerves continuously have reduced the arterial pressure.

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The objective of this conference is to review our experience with intermittent electrical stimulation of the carotid sinus nerves in the management of intractable angina pectoris and supraventricular tachycardia. Our interest in the use of this approach for the treatment of angina arose from a series of investigations on the determinants of myocardial oxygen consumption. These investigations were recently reviewed elsewhere<sup>8</sup>; briefly, however, they demonstrated that the oxygen demands of the heart are not simply a function of the external work of the heart, that is, the product of arterial pressure and cardiac output. Rather, the development by the ventricles of pressure (more strictly speaking, tension) has a relatively high oxygen cost, while the cardiac output is a far less important determinant of myocardial oxygen consumption. In addition to tension, the level of myocardial contractility, that is, the inotropic or contractile state of the myocardium, is a second important determinant of the heart's oxygen needs. A third factor, of course, is that the heart's oxygen consumption is a function of cardiac frequency—the number of times the heart contracts per unit of time. A number of other physiologic variables have been studied, but none even approach in importance the three factors mentioned above—tension, contractility and heart rate—in the control of myocardial oxygen consumption.

It is generally appreciated that angina pectoris results from an imbalance between the heart's oxygen needs and the oxygen supply. In the large majority of patients this imbalance results from a defect in the delivery of oxygen to the myocardium as a consequence of obstruction in the coronary vascular bed secondary to atherosclerosis. In other patients, however, this imbalance results to a significant extent from increased myocardial oxygen demands, as occurs in aortic stenosis, thyrotoxicosis and tachycardia. Ideal therapy for angina pectoris would be to restore the balance between supply and demand in as physiologic a manner as possible—by increasing oxygen delivery when it is limited, and by reducing oxygen demands when these are excessive. In practice, however, this has been difficult to achieve, particularly in patients with diffuse, severe atherosclerosis.

With this understanding of the determinants of myocardial oxygen consumption in mind, we at first sought to relieve angina pectoris by reducing myocardial oxygen consumption through stimula-

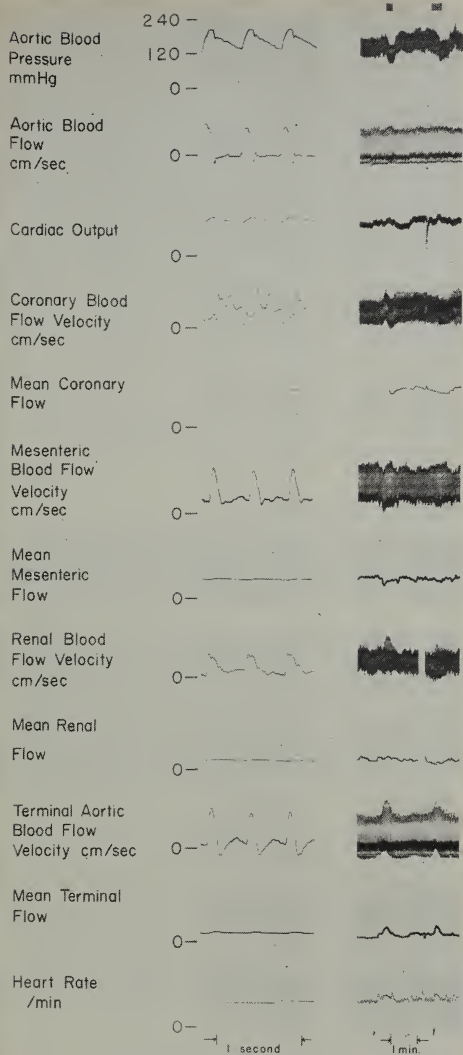
tion of the vagus nerve. In collaboration with Drs. Gerald Glick and Andrew Wechsler, we placed radiofrequency stimulators on the right vagus nerve of a group of dogs and, after they recovered from the procedure, observed that we could reduce their heart rates to almost any desired level when they were studied under general anesthesia. However, when the dogs were conscious, electrical stimulation of the vagus nerve always produced serious side effects—coughing, salivating, vomiting—apparently because of activation of fibers in addition to efferent cardiac parasympathetics. We then directed our efforts to electrical stimulation of the carotid sinus nerves, because, as indicated above, activation of these nerves results in reflex reductions of heart rate, arterial pressure and myocardial contractility, the three prime determinants of myocardial oxygen consumption. The experimental results were far more promising and we then studied a group of dogs for periods up to one year and observed that they tolerated electrical stimulation of the carotid sinus nerves without significant deleterious side effects. The observation that manual stimulation of the carotid sinuses can abolish attacks of angina<sup>9</sup> and that in fact Lown and Levine<sup>10</sup> have proposed this as a diagnostic test for angina encouraged us to apply this method clinically in patients with angina pectoris.

Before summarizing the results of carotid sinus nerve stimulation in patients with angina pectoris, Dr. Vatner will describe studies currently in progress in our laboratory on the hemodynamic changes resulting from brief periods of electrical stimulation of the carotid sinus nerves in dogs.

### Hemodynamic Changes

DR. STEPHEN F. VATNER:\* Our interest in studying the effects of carotid sinus nerve stimulation in the conscious animal arose from the fact that the carotid sinus reflex is of preeminent importance in the reflex control of arterial pressure and heart rate. Although numerous investigations into the effects of carotid sinus nerve stimulation have been carried out in anesthetized animals,<sup>1</sup> little information on the circulatory effects of stimulating these nerves is available in intact unanesthetized animals. General anesthesia has profound influence on circulatory regulation by the carotid sinus

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**Figure 1.**—The effects of carotid sinus nerve stimulation on aortic blood pressure, ascending aortic blood flow, left circumflex coronary blood flow, mesenteric blood flow, renal blood flow, terminal aortic blood flow and heart rate. The periods of stimulation are presented by the black bars at the top. Left panel: Tracing at rapid paper speed. Right panel: Tracing at slow paper speed. All blood flows are shown as instantaneous velocity and mean flow.

nerves.<sup>11</sup> Therefore, we wished to examine the effects of carotid sinus nerve stimulation in healthy animals not under the influence of anesthesia. In view of the increasing clinical applications of carotid sinus nerve stimulation in patients with angina

and hypertension, as described by Dr. Braunwald, this investigation in conscious dogs was considered to be particularly important since it might provide information about the carotid sinus reflex which cannot be readily obtained in man. In studies carried out in collaboration with Mr. Dean Franklin and Drs. R. Van Citters and E. Braunwald<sup>11-13</sup> we determined the effects of carotid sinus nerve stimulation on the responses of arterial blood pressure, heart rate, cardiac output and blood flow distribution in the iliac, renal, mesenteric and left circumflex coronary beds.

With the animals under sodium pentobarbital anesthesia, pulsed ultrasonic or Doppler ultrasonic flow probes were placed on the ascending aorta and the left circumflex coronary artery, as well as on the mesenteric, renal and iliac arteries, and miniature solid state pressure gauges were placed in the central aorta. Electrodes were placed on both carotid sinus nerves. One to four weeks after recovery from the operation, with the animals apparently well, experiments were performed in 12 dogs and two baboons. A radiofrequency pacemaker\* identical to that used in the clinical studies was used to stimulate the nerves for 30-second periods. The experiments in which the pulsed ultrasonic flowmeter was used were conducted in the laboratory; the battery-operated Doppler ultrasonic flowmeter could be placed in saddle bags so that flow and pressure could be telemetered without the animals being tethered (Figure 1).

Carotid sinus nerve stimulation resulted in an initial fall in aortic pressure, the decrease averaging 20 to 35 percent of resting control levels. However, pressure began to return to control levels even while stimulation was continued and reached control levels shortly after stimulation ceased. Surprisingly, heart rate decreased only slightly, by 12 percent of control, during the initial phase of stimulation and returned to control levels after only about 10 seconds of stimulation, while arterial pressure continued to fall. In some animals heart rate actually increased to above control levels with continuation of stimulation for periods exceeding 20 seconds. After an initial decrease of approximately 10 percent, cardiac output returned to control levels during carotid sinus nerve stimulation. Thus, since arterial pressure decreased significantly, calculated peripheral vascular resistance declined.

\* Manufactured by Medtronic, Inc., Minneapolis.

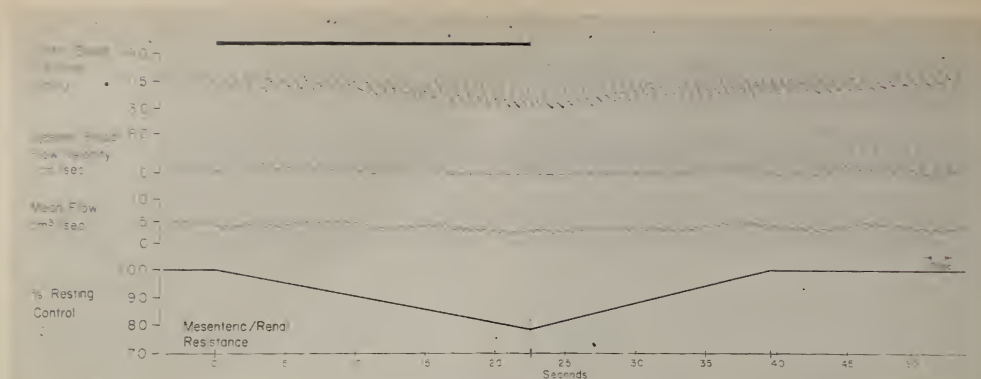


Figure 2.—The effects of carotid sinus nerve stimulation on aortic blood pressure and mesenteric blood flow. The graph at the bottom illustrates the average decreases in calculated resistance from control levels in both the mesenteric and renal beds in six dogs. The black bar at the top represents the period of carotid sinus nerve stimulation.

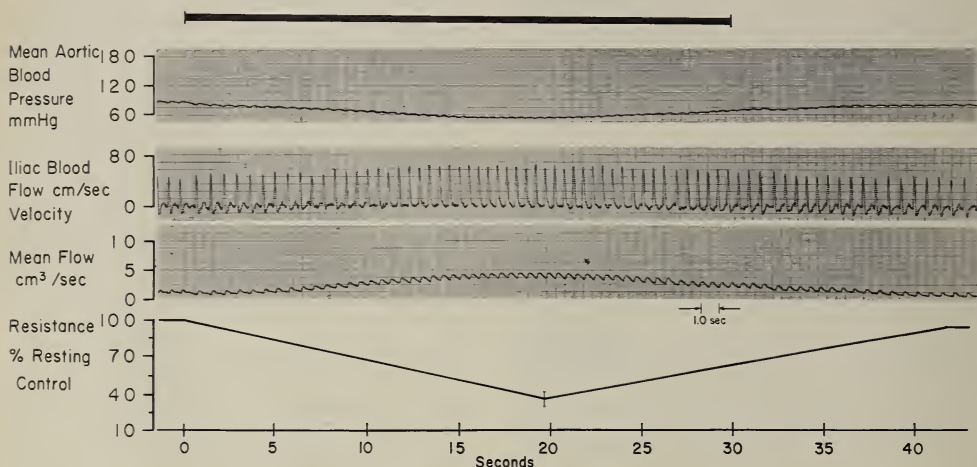


Figure 3.—The effects of carotid sinus nerve stimulation on the iliac circulation. The black bar at the top represents the 30-second period of stimulation. The average maximum decrease in calculated resistance in the iliac bed in six dogs from central levels is demonstrated by the graph at the bottom.

The mesenteric and renal beds responded in a similar manner (Figure 2); in both beds flow decreased during carotid sinus nerve stimulation, but not as much as pressure, resulting in a net decline in calculated vascular resistance in these two beds by approximately 20 percent of control. In contrast to the other beds which we studied, flow to the hind limbs uniformly increased during carotid sinus stimulation, sometimes up to four times the control level, despite the decrease in

arterial pressure (Figure 3). Thus, far greater dilatation occurred in the iliac than in any of the other vascular beds, amounting to a 60 percent to 70 percent decrease in calculated vascular resistance.

We anticipated that carotid sinus nerve stimulation would cause no change or perhaps only a slight increase in coronary vascular resistance, since carotid sinus nerve stimulation reduces the metabolic requirements of the heart by lowering arterial pressure, heart rate and contractility, and



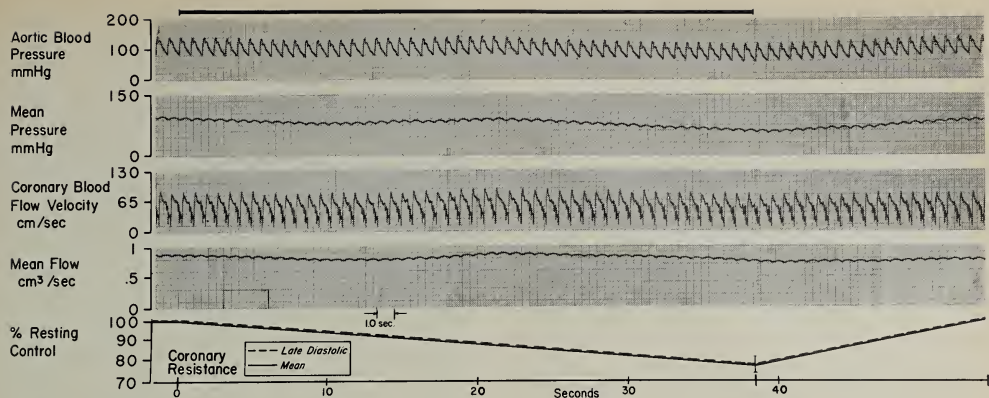


Figure 4.—The effects of carotid sinus nerve stimulation on aortic pressure and left circumflex coronary artery blood flow. The graph at the bottom represents the average maximum decrease in calculated mean and late diastolic coronary resistances in six dogs. The black bar at the top represents the period of nerve stimulation.

since coronary vascular resistance is determined largely by and is inversely related to myocardial oxygen consumption. We were therefore somewhat surprised to find that coronary blood flow remained constant, decreased only slightly, or in some experiments actually increased, and calculated coronary vascular resistance declined by 20 to 25 percent (Figure 4). Subsequent studies in dogs treated with various autonomic blocking agents—atropine, propranolol and guanethidine—revealed that the reduction in coronary vascular resistance induced by carotid sinus nerve stimulation was mediated primarily by a reduction of sympathetic vasoconstrictor impulses to the coronary bed.

Thus, we have found that carotid sinus nerve stimulation in conscious animals produces an expected decrease in arterial pressure, surprisingly little bradycardia, and significant dilatation in all beds studied. The greatest reductions in calculated resistance occurred in the muscular circulation, where flow actually increased while arterial pressure decreased. Of greatest interest and potential clinical significance is the finding that carotid sinus nerve stimulation causes a decrease in calculated coronary vascular resistance. The fall in vascular resistance in all beds appears to be due to release of sympathetic constrictor tone, while the bradycardia is due more to vagal stimulation than to decreased sympathetic activation.

DR. E. BRAUNWALD: Before the performance of the experiments described by Dr. Vatner, it was

our impression that the relief of angina resulting from carotid sinus nerve stimulation resulted entirely from a reduction of myocardial oxygen requirements, and the creation therefore of a more favorable relation between myocardial oxygen supply and requirements. Now, we must also consider the possibility that coronary vasodilatation occurs. The observations in conscious dogs just described also complement those which we made in patients together with Dr. Stephen E. Epstein and others.<sup>14</sup> The effects of carotid sinus nerve stimulation were studied at rest and during a mild level of supine bicycle exercise in seven patients in whom stimulators had been implanted for the treatment of angina pectoris. At rest, carotid sinus nerve stimulation produced a fall in mean arterial pressure averaging 23 percent, an 8 percent decrease in cardiac output, and a 9 percent decline in heart rate. Total peripheral resistance fell by 14 percent and forearm vascular resistance by 16 percent. During exercise with carotid sinus nerve stimulation, mean arterial pressure fell by 16 percent but, interestingly, no significant change occurred in the cardiac output, and the decreases in heart rate were very small. Thus, the fall in arterial pressure could be attributed to a reflexly induced decrease in peripheral vascular resistance. No changes in venous tone, central venous pressure, or the maximum transverse end-diastolic diameter of the heart were produced by stimulation, either at rest or during exercise. Thus, at rest, carotid sinus nerve stimulation reduces mean arterial pressure by reflexly decreasing both vascular resistance and car-

diac output, while during exercise, the diminution in cardiac output no longer occurs. The venous system does not appear to participate in reflexes activated by carotid sinus nerve stimulation.

Our clinical experiences with carotid sinus nerve stimulation in patients with incapacitating angina began in June 1967. We have used this treatment in a total of 22 patients with angina pectoris, first at the National Heart Institute and more recently at the University of California, San Diego. The presence of severe coronary artery disease in these patients was proved by coronary arteriography, and in all of these patients was found to be unresponsive to intensive medical management. I shall now ask Dr. Nina S. Braunwald to describe the device used and the operative technique employed.

### Operative Implantation of Electrodes

DR. N. S. BRAUNWALD:\* The carotid sinus nerves are stimulated bilaterally by bipolar platinum electrodes connected by stainless-steel wires to a receiving unit implanted subcutaneously in the anterior chest wall. The transmitting unit is worn externally and generates 20 to 80 radiofrequency pulses/sec., 0.3 msec in duration and 0.5 to 8 volts in amplitude. The pulses from the signal generator are transmitted by an induction coil that is placed on the skin directly overlying the implanted receiving unit. The patient activates the transmitting unit at will by an on-off switch (Figure 5).

The anesthetic and surgical techniques have been described in detail elsewhere.<sup>15,16</sup> Briefly, however, all drugs are discontinued one to two days before operation. Following premedication, the patients are taken to the operating room where an intra-arterial needle is introduced into the radial artery for constant monitoring of arterial pressure. The heart rate and electrocardiogram are also monitored continuously and any fluctuations are treated immediately with appropriate drug therapy. Following induction of general anesthesia, a transverse incision is made below the clavicle on the anterior chest wall and a small pocket is developed to permit implantation of the receiver. Two transverse incisions are then made below the mandible at the level of the hyoid bone, the carotid sheath is entered and the carotid bulb identified. Umbilical tapes are placed about the internal and external carotid arteries. The carotid sinus nerve



Figure 5.—The radiofrequency stimulator used in the treatment of angina pectoris. The transmitter and antenna are worn externally and are shown at the right. The implanted receiver unit is seen at the top.

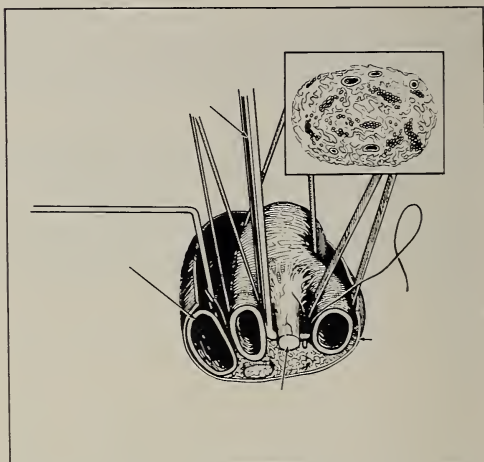


Figure 6.—The carotid sinus nerve which lies in the angle between the internal and external carotid arteries is isolated together with its nutrient vessels before placement of the electrodes about the nerve.

is identified in the bundle of tissue between these two vessels. A heavy silk suture is placed about the nerve, taking care not to isolate the carotid sinus nerve from its nutrient vessels in order to insure permanent viability of the nerve (Figure 6). Also, the terminal branches of the nerve should not be disturbed as they spread out over the carotid bulb, lest the structure be denervated. Dissection of the nerve 1 to 2 cm proximal to the carotid bifurcation insures that these fibers will remain intact. An effort is made to identify the hypo-

\* Associate Professor, Department of Surgery, University of California, San Diego.



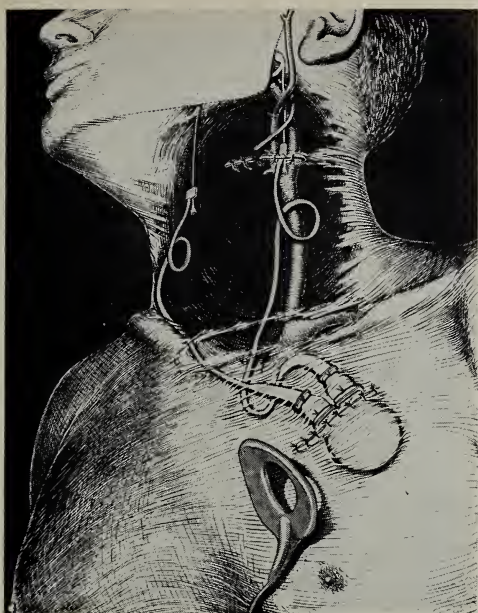


Figure 7.—The receiver is positioned on the anterior chest wall and is connected to the electrode units which are secured about the carotid sinus nerves on each side of the neck.

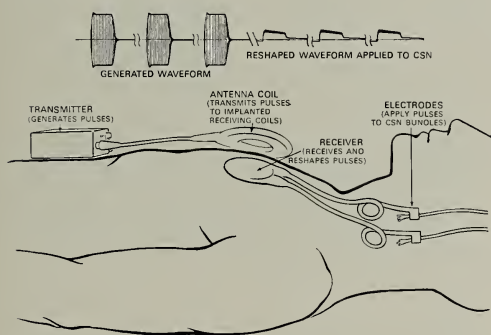


Figure 8.—The shape of the waveform generated by the externally worn transmitter is shown at top of picture. It is generated when the patient places the antenna coil over the receiver and actuates the on-off switch. CSN=carotid sinus nerve.

glossal nerve as it crosses the upper portion of the field. Whenever possible this structure must be protected and undue traction on this nerve assiduously avoided.

Tunnels are then made on each side of the neck with a blunt instrument, connecting the submandibular incisions with the infraclavicular pocket.

Both electrodes are passed through the tunnels inside Penrose drains. The silicone jackets of the electrodes are opened and positioned about the carotid sinus nerve before securing the electrodes (Figure 7). The response to a test dose of current is determined to make sure that the unit is functioning satisfactorily, as evidenced by a reduction in systolic blood pressure of 15 to 20 mm of mercury and a slowing of the heart rate by 5 to 10 beats per minute. The silicone jackets around the electrodes are sutured closed and the incisions are also closed, leaving adequate slack loops of the electrodes in the neck to allow for full range of motion of the head and neck postoperatively (Figure 8).

A series of drug solutions is made up before operation and used throughout the procedure to maintain the hemodynamic status of the patient as close to the preoperative level as possible. If the heart rate falls below 55 beats per minute, atropine is administered. Hypotension associated with a normal or fast heart rate is controlled with phenylephrine. If hypotension associated with a slow heart rate develops and is not controlled with atropine, isoproterenol is administered immediately. The systolic pressure is not allowed to fall more than 10 mm of mercury below the patient's usual level. Hypertension is treated with trimethaphan (Arfonad®). Lidocaine hydrochloride is given intravenously for ventricular irritability.

It has been observed that patients complain of a variety of side effects postoperatively, including pain in the operative area and coughing, if the stimulator is used before healing is complete. This is probably due to radiation of the electrical current to branches of the local sensory nerves in the dissected area. Therefore, three to four weeks are allowed to elapse before the unit is activated. During the initial testing period an intensity of stimulation is selected which causes a fall in arterial pressure to a level 15 to 20 mm of mercury below the control, while at the same time relieving the angina.

Two deaths occurred in the immediate postoperative period in our first four patients. These resulted from massive myocardial infarctions; one was due to an episode of bradycardia and hypotension intraoperatively in response to traction on a sensitive carotid sinus nerve. The other occurred in a patient in whom hypoxemia developed following extubation while being moved from the ope-



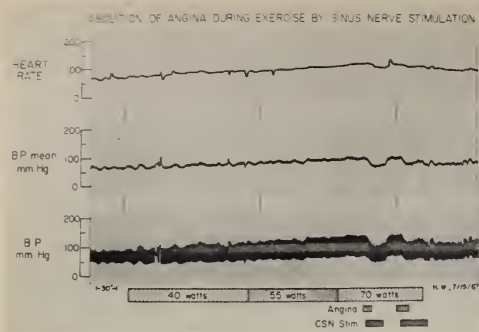


Figure 9.—Representative tracing showing the abolition of angina during exercise by sinus nerve stimulation. The onset of angina occurred during exercise performed at 70 watts. At this point the stimulator was turned on, and heart rate and arterial pressure fell. This was immediately followed by complete cessation of the angina. The stimulator was then turned off. The heart rate and blood pressure rose, and angina recurred. Turning on the stimulator again resulted in decreases in heart rate and arterial pressure and disappearance of the chest pain. (Reproduced by permission from New England Journal of Medicine 277:1278, 1967.)

rating room to the recovery room. The subsequent 18 patients have all survived the operation. Bilateral hypoglossal nerve paralysis occurred in one patient as a result of undue traction on the nerve, and temporary unilateral paralysis was noted in two others. In all instances there was complete recovery over the ensuing months.

The candidates for insertion of the carotid sinus stimulator represent an especially high risk group of patients even for a relatively simple operation because of their far advanced coronary artery disease. Hence, if the operative mortality is to be kept to a minimum, particular attention must be paid to even the most minute details of intraoperative and postoperative management. Thus, the blood pressure and heart rate must not be allowed to deviate from the normal. Oxygen saturation must be optimally maintained at all times. This can be facilitated by measuring blood gases regularly and leaving the endotracheal tube in place until adequate ventilation is assured.

## Results

DR. E. BRAUNWALD: Fifteen of the 20 surviving patients experienced striking symptomatic improvement.<sup>17,18</sup> They reported that they could terminate all or almost all episodes of angina by carotid sinus nerve stimulation. Prophylactic use of the stimulator—that is, activating the device

## PREVENTION BY SINUS NERVE STIMULATION OF EXERCISE INDUCED ANGINA

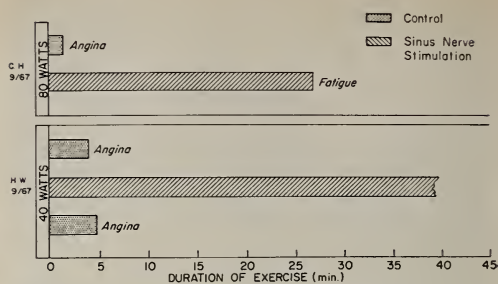


Figure 10.—Effect of carotid sinus nerve stimulation on the capacity of two patients to perform a level of exercise that, in the absence of stimulation, consistently produced angina in less than 5 minutes. (Reproduced by permission from New England Journal of Medicine 277:1278, 1967.)

## EFFECT OF SINUS NERVE STIMULATION ON EXERCISE CAPACITY IN TWO PATIENTS

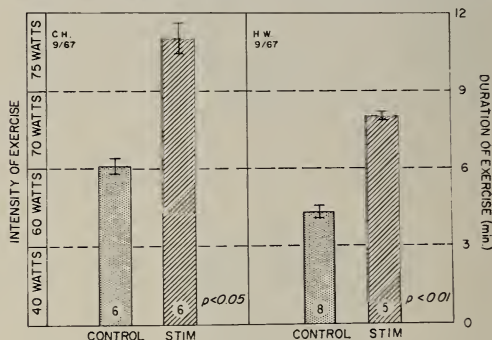


Figure 11.—Effect of carotid sinus nerve stimulation on the intensity of exercise that could be achieved before the development of anginal pain. The exercise load was increased every 3 minutes, and exercise was stopped at the onset of angina. The number of trials is shown at the bottom of the vertical bars. (Reproduced by permission from New England Journal of Medicine 277:1278, 1967.)

before exertion which would ordinarily produce angina—allows them to perform more strenuous activities without the occurrence of angina and the consumption of nitroglycerine was decidedly reduced (Figures 9, 10, 11). Two patients did not appear to benefit from the stimulator while two experienced only moderate relief of symptoms. One patient was operated upon too recently to allow evaluation. In the majority of patients exhibiting ST-segment depression during exercise, prophylactic activation of the stimulator before exercise caused changes in the ST segment to begin later during the course of exercise, and at any given

time during exercise the ST segment depression was less than without stimulation.<sup>18</sup>

Stimulation of the carotid sinus nerves appears to be superior to nitroglycerin for several reasons. It is more rapid in onset, and since relief of angina is complete within seconds, the patients are not forced to interrupt the activity that precipitated the angina; it is more reliable in consistently aborting each anginal episode and it is not accompanied by some of the undesirable side effects of nitroglycerin, such as headache, a pounding pulse and a feeling of faintness in the upright position. In addition, this method of relieving anginal attacks seems to be preferable to the chronic administration of beta-adrenergic receptor blocking agents since sinus nerve stimulation deprives the heart of sympathetic support only intermittently—that is, at the time angina actually occurs or is likely to occur. However, the combined use of the blocking agents and intermittent sinus stimulation may be more effective in the control of angina than either one alone. Another advantage of sinus nerve stimulation is that because of its predictability and reliability it allows initiation of a program of increasing physical activity in patients with severe coronary artery disease. Such a program may help to induce formation of collateral vessels and thereby alter favorably the natural history of the illness.

Although these results are promising, it must be emphasized that carotid sinus nerve stimulation is not without hazard. Insertion of the electrodes and the receiving unit requires an operation under general anesthesia, a procedure that carries some risk in patients with serious coronary artery disease. However, the development of a plan for the intraoperative and early postoperative management of these patients<sup>15,16</sup> and careful adherence to this plan, should minimize future risks. It should be emphasized that not all patients with angina pectoris are candidates for this method of treatment since most of them experience relief by medical management alone. However, those patients who are severely incapacitated by angina despite optimal medical management should, I believe, be considered for carotid sinus nerve stimulator implantation. Also, it is clear that there is no incompatibility between carotid sinus nerve stimulation and other operative methods for treating angina. Thus, in the event of failure of nerve stimulation, a revascularization procedure or direct bypass of the coronary obstruction could still be carried out

later. Also, and in our experience much more commonly, the reverse may be the case and patients who have not benefited from myocardial revascularization are considered for insertion of a carotid sinus nerve stimulator. It is our current policy in patients with intractable angina to consider carotid sinus nerve stimulation first, since it is a simpler procedure, and to hold one of the other surgical procedures in reserve.

As indicated earlier in the conference, manual stimulation of the carotid sinuses frequently abolishes attacks of supraventricular tachycardia. Dr. Sobel will now describe the application of electrical stimulation of the carotid sinus nerves in a patient with this condition.

### Use of Stimulation in Supraventricular Tachycardia

DR. BURTON E. SOBEL\*: On the basis of observations in patients with angina pectoris and patients with hypertension the efficacy of implanted radio-frequency carotid sinus nerve stimulators in providing a safe means for initiating reflex vagal activity is now established. Electrical stimulation of the carotid sinus nerves offers several advantages over manual stimulation to produce reflex activation of the vagus nerves. The possibility of trauma to the carotid artery is avoided, as is the risk of dislodging a thrombus from the vessel and of interference with cerebral blood flow. Accordingly, we elected to use this approach in a patient with incapacitating, recurrent supraventricular tachycardia resistant to conventional methods of treatment.<sup>19</sup>

The patient was a 69-year-old man with a 21-year history of well documented, recurrent supraventricular tachycardia. Some episodes were clearly paroxysmal atrial tachycardia while others were paroxysmal nodal tachycardia. During the year preceding admission, the bouts of arrhythmia increased in frequency and severity. Attacks lasted for periods of as little as 10 minutes to as much as 17 hours and occurred seven to ten times a week. They were accompanied by diaphoresis and often followed by chest pain. Treatment such as manual pressure on the carotid sinus or administration of intramuscular metaraminol became less effective in terminating attacks during the year preceding admission. A vigorous medical regimen, including large doses of procaine amide and quin-

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idine, and combinations of other agents including digitalis, diphenylhydantoin, atropine, and propranolol were ineffective in preventing attacks. Physical findings at the time of admission were unremarkable, as were the usual laboratory studies. The electrocardiogram showed left axis deviation, parietal block, a wandering atrial pacemaker, and evidence of an old anteroseptal myocardial infarction.

**D**uring the first few weeks following implantation of the stimulator several episodes of paroxysmal supraventricular tachycardia occurred and were successfully terminated by activation of the carotid sinus nerve stimulator. However, when hypotension accompanied the arrhythmia, the carotid sinus nerve stimulator was effective only when systemic arterial pressure had been elevated with phenylephrine. The need for additional pharmacologic therapy rapidly diminished and after the second postoperative month activation of the stimulator alone was consistently effective in terminating bouts of supraventricular tachycardia.

More recently we treated a 65-year-old woman with recurrent atrial tachycardia with a carotid sinus stimulator. Although it is too early for definitive evaluation, the initial results are also encouraging; the patient stopped her last episode of tachycardia with the stimulator.

The mechanism responsible for paroxysmal supraventricular tachycardia appears to be either rapid discharge of an ectopic pacemaker or reciprocal beating. In either case, vagal stimulation has a salutary effect by diminishing automaticity or slowing conduction through the atrioventricular junction. Our initial experience with this therapeutic approach has been gratifying and the use of a stimulator avoids the small but definite risk attendant on repetitive manual carotid sinus massage. Since the radiofrequency stimulator can be activated by the patient at will, and since patients are immediately aware of the onset of supraventricular tachycardia, radiofrequency stimulation of the carotid sinus nerves offers obvious advantages in the treatment of this arrhythmia. Other methods of producing reflex vagal stimulation, such as the administration of pressor drugs, may be associated with a cerebrovascular accident, myocardial damage, or pulmonary edema due to transient but pronounced systemic arterial hypertension. However, it must be acknowledged that the long range benefits and hazards of radiofrequency stimula-

tion of the carotid sinus nerves in the treatment of supraventricular tachycardia are yet to be defined.


**DR. E. BRAUNWALD:** In conclusion, while considerable information concerning the function of the carotid sinus reflex in anesthetized animals has been available, the precise role of this reflex in circulatory control in intact conscious animals and in man had not been clarified. The experiments on conscious dogs and the clinical observations on patients with implanted carotid sinus nerve stimulators described in this conference are providing an increased understanding of this important reflex. It appears that the ability to activate this reflex in patients allows control of intractable angina pectoris and of recurrent supraventricular tachycardia. The early results have been sufficiently encouraging to warrant continued trial of this new mode of therapy.

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# RELEVANCE



## *today and tomorrow*

## in Medical Education

### A FORUM WITH A PURPOSE

*Students of today question the relevance of much of their formal education. In medical schools the concern is particularly with the relevance of the educational experience to the professional commitment in modern society. To engender discussion of the subject, CALIFORNIA MEDICINE in its January issue printed eight essays by authors known to have keen interest in the subject.*

*Readers in California and elsewhere are invited to take part in a continuation of the forum in succeeding issues. The following are contributions selected from those received to date. Others will be published in the months ahead. At an appropriate time the material will be collated and, if feasible, the distillate will be prepared in the form of a statement.*

*If you have thoughts on the subject, just address them to the editors of CALIFORNIA MEDICINE, 693 Sutter Street, San Francisco, California, 94102. Keep your essays short, please.*

#### CHEVES McCORD SMYTHE, M.D.

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Associate Director, Association of  
American Medical Colleges*

FROM THE CACOPHONY on relevance one can distill a partial list of its attributes which runs along the following lines. Among other things relevance seems to mean less basic science, earlier introduction to clinical medicine, more and much better preventive medicine, more mass medicine, a greater voice in administrative affairs, a demand for instant investment of the resources—human, physical, facilities and money—of the academic medical center into a frontal, and not necessarily well thought out, attack on the myriad and very pressing sociologic, in addition to medical problems, of the poor, especially the black, urban poor. Relevance also calls for a reordering of priorities with more precise decisions on where educational and medical energies should be applied, expansion of educational opportunity, and a different conception of the relation between the teaching hospital and its supporting population. Relevance has come to mean reform in medical education.

Although some look back nostalgically to the status quo ante, there are no very enthusiastic defenders of the status quo. Therefore, the problem facing those who are responsible for the direction of our academic medical centers is not whether to become more relevant or not, but of how to see their institutions through a transitional period into what will be a very different medical education and medical care system. These institutions are presented with an

enormous list of demands and opportunities. At the same time they must maintain their ongoing programs. That prevention of atherosclerosis is more desirable than its treatment, does not abolish the necessity for maintaining today's coronary care units. That it is deplorable that there are no adequate community services for the poor and that it is obvious something must be done about it, in no way lessens the need to provide some help to the overwhelming numbers of people coming to the emergency room tonight. Meeting today's obligations requires energy and time which is then not available to accomplish more or less obvious reforms. This point must be made because the movement toward reform is unthinkable without simultaneously offering devoted attention to those who are now enrolled in and cared for in the teaching institutions. If the medical centers responded to every demand made on them, the result would be a disaster composed of an ever-lengthening list of half-done assignments or unaccomplished objectives.

The schools must have some method of determining what is indeed most relevant for them. In other terms, they must establish policies from which judgments or priorities are set.

One such grouping of general principles might include the following:

- Medical schools are primarily in the education and not the service business. There is little to indicate they are superior managers. Other units of society have more experience and are probably more proficient at running large service-providing systems.

• The goal of education is to induce a different level of behavior in the learner. Both learner and teacher must act in collusion for optimal, efficient, and effective realization of that goal. That they should work together to define the altered level of behavior desired makes excellent sense.

• The fact that the medical schools are inducing levels of behavior in their students focuses on the schools the need to conceptualize and to state in plain terms the medical care system in which they expect their graduates to work. Each and every school must do this for its students' and its own sake, and once again, that many should participate in this process makes excellent sense.

• What the doctor needs to know has become such an overwhelming question that mercifully it must be supplanted by the more important question, what does a doctor have to be able to do? Five basic abilities are suggested as necessary:

- (a) He must understand our society and culture well enough to adapt to it, change with it, and establish meaningful relationships with the people he meets in it.
- (b) He must understand the language, mental processes, and the complex culture of medicine well enough to move readily through it. He must be able to manipulate this culture for the benefit of his patients.
- (c) He must be able to formulate and solve problems and make and act on decisions arising from these solutions.
- (d) He must possess the manual and craft skills necessary for his profession.
- (e) He must be able to understand the language and logic of science so that he may continue to learn.

Medical education should become more concerned with what medical students can do and perhaps less concerned with what they know.

The greatest irrelevance of which medical education can be guilty is to dissipate its energies into a series of good and important works not essential to its primary role and responsibility in society. Fulfilling that primary role is difficult and energy-consuming enough. First things do indeed come first, and secondary things never, if a system is to be effective. Thus medical education, to be relevant, must define its essential principles and test each of the bewildering array of demands made on it against such carefully constructed policies.

## EUGENE S. OGROD, II, B.A.

*Stanford*

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IT IS THE CURRENT medical education fashion to talk of the "whole man" and "health in its broadest definition." Yet we as a profession are very insecure with these concepts. Perhaps this insecurity is due to the disparity between what we would like to be and what we think we really are. However, we set other artificial barriers which contribute to this insecurity.

In teaching about the whole man we must accept that all parts of man's life are legitimately subject to medical scrutiny. We should not fear probing into all aspects of man's behavior and environment. The knowledge thus gained should be easily available for others to learn. All of this means we must accept the limitations of our own knowledge and seek the cooperation of people in non-medical fields in the medical educational process.

The rapid expansion of medical knowledge has given birth to the specialist. The broad definition of health is developing a new set of medico-behavioral specialists. Physicians from the older specialties as well as those just graduating are carving out new areas of "medical" knowl-

edge in social psychology, population genetics, economics, political science, anthropology, computer science and mathematics. At the same time the classic basic medical knowledge is still expanding at an exponential rate. Gone is the day when a physician can know it all. This perhaps is a major factor in the disappearance of the GP. We may see the day when Mr. Jones refers to his physician and means a group of four or five men who function as a professional entity.

In this developing complex system of the whole man, broad definition of health and rapid expansion of medical knowledge with new specialties, how can you prepare a medical student? What is relevant? The answer is, everything. The M.D. is the most versatile degree in the world, with limitless shades of opportunities. Each of these opportunities needs a different background, and though the differences may be slight they can also be very great.

We have attempted thus far to prepare the medical student in a rigid prescribed system of courses. Stanford University and other medical schools are developing what is called the elective curriculum. That is a misnomer. In reality these new programs are attempts at a flexible, sliding curriculum which can more easily accommodate the student's varied interests and the profession's varied needs. The flexible curriculum concept has several assumptions and ground rules.

• The student must be motivated and challenged to learn, not spoon-fed by lecture.

• The importance of the process is to provide background familiarity and, above all, learning skills which the student can use throughout his career.

• How the student acquires his basic knowledge or in what order is largely irrelevant.

• In-depth study should be allowed as the student is motivated.

• There should be increasing integration of courses as well as elimination of the arbitrary preclinical and clinical programs division.

• There must be multiple methods of teaching, learning, information storage and retrieval.

• There should be available a wide range of course offerings and multiple programs leading to the M.D.

The essence is flexibility with emphasis on obtaining a range of knowledge in a variety of learning situations.

Considering the above type of program, I feel the two-year medical school which has been proposed as a means to reduce the physician shortage is at a disadvantage. It only continues the present rigid system.

The fluid curriculum provides for an interlacing of clinical and non-clinical material. Early patient contact provides the beginning student with some answers as to why he is ploughing through all this material. It also begins to give him some yardstick so that *he* can begin to evaluate what is relevant. On the other hand the "clinical" student is able to dip back into basic science seminars as he sees the need to fill in areas of knowledge or as he develops new interests.

Part and parcel to the issue of relevancy is the presentation of knowledge and information retrieval. Teaching methods must be reexamined. Extraction of medical knowledge from the medical literature (the journal jungle) involves vast amounts of time. Now even the *Index Medicus* takes a guide book to use. Getting the basic knowledge can be difficult even after it has been judged relevant. This complexity of the literature inhibits the student's curiosity and motivation to learn. It is no longer a matter of simply studiously going through a textbook but often hours of search through many possibly relevant articles. Dependence on faculty for suggestions and clues is totally inadequate.

The medical student of today must have development of learning skills, adequate means of information retrieval, clinical exposure, integration of course material, input from many related fields, contact with practitioners and organized medicine, knowledge of current problems in medicine. None of this can be done in a rigid course of study. But even in our enthusiasm for the new medicine and its broad interest in the behavior of man, we should not allow



a pendulum-swing to saddle the student with trying to learn of all of these aspects of man. This is just as bad as forcing tons of basic science data upon him. As we have done in other fields with the older branches of medicine, we will develop specialists who will work for the profession in the areas of community medicine, political science, economics, computer science, etc. Thus, we should not try to list rigidly what is relevant but remain flexible enough so that the student can learn where he is curious and society can encourage where it has need. This is essential because we plan for a tomorrow, and we do not know what tomorrow will be.

## EINAR O. MOHN

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IF MEDICAL STUDENTS today have any sense of humor—and heaven help us if they don't—they must be amused at the sudden concerns of their schools over "relevance." After all, medical schools have always been relevant to something. For many years, the chief interests of the schools seemed to be their alumni and local medical societies. When federal research money became available, medical schools began to practice the art of grantsmanship and rehearse the strange language of federal budgets and appropriations. To find points of relevance, look for sources of income. Medical schools are not alone in this characteristic, obviously, but now that health care has been adopted as a social and economic right, the medical school's sensitivity to purse strings over patients seems especially inappropriate.

Because while the medical schools of California have grown large and, in their own way, prolific, they have seemed apart from the world. Within the shadows of most laboratory buildings in California are people who cannot afford even minimum levels of medical care. Within minutes of the buildings where medical miracles are commonplace, live mothers who bring up their children without benefit of physician care before or after birth.

Doctors, dentists, and hospitals are stacked on top of each other in neighborhoods in our state while lower income areas are filled with a great emptiness in services or help.

While nearly every reasonable observer of the health industry now recognizes that our manpower shortages can't possibly be overcome without developing organized health delivery systems, most medical schools still train physicians to practice as though they were that solitary doctor in the submarine who has to take out an appendix with a kitchen knife and his bare hands.

Speaking as a consumer, I am glad to observe student concerns with these and other untimely features of higher medical education. I doubt that adding a few courses here and there and patching up the curriculum will satisfy the demands of the students, any more than such steps will satisfy the health needs of our society.

Rather than merely reacting to student demands, I suggest the schools begin looking upon those demands as the early expression of a wider discontent, namely the public's needs for medical schools to become engaged in the battle for a healthier society at the front lines. Bringing up the rear behind traditional medical practice will neither meet the needs nor pacify the students.

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I'VE READ WITH much interest the articles in the January issue of CALIFORNIA MEDICINE appearing in the forum on "Relevance for Today and Tomorrow in Medical Education." I was amazed, however, not to find the terms *family medicine* and *family practice* and I began to wonder if using them was against the rules. Upon learning that this was not the case, I decided to discuss briefly the recent family practice movement in relation to the subject of the forum.

I've selected a few pertinent sentences from the statements of several of the initial participants of the forum:

Dr. Haviland: "Students should have first-hand experience with providing health services in a variety of settings." And, "... students must be exposed adequately not only to scientific facts and their application, but also to scientific approaches to society's and people's problems in the health fields."

Dr. Leymaster hears students saying: "Allow us to test its [science's] pertinence early in our medical school career, with patients, with social problems, with community experiences." And, "Why can't a profession capable of transplanting hearts do a better job of relieving anxiety and fear?"

Dr. Millis: "... medical practice has advanced a great deal for the 10 percent of patients who are critically ill but it has not advanced comparably for those parts of health care which affect most or all of the citizens of the country." And, "The environment [of the university hospital] is not one of comprehensive and continuing health care." And, "The students' attention is concentrated upon disease rather than health."

Student Stalcup: "I believe that medical students, like those who preceded them, are being trained to treat symptoms of disease and given little insight into the processes which produced the disease."

Student Martin: "In the case of medical schools, the larger goal would seem to be the actualization of a health care system where adequate quality care would be available to all people in America and where health, not disease, would be the primary concern of health professionals." And, "It is impossible to reconcile the acute, episodic and fragmented clinical service teaching system with either the needs of the community or the needs of the medical students who will be practicing in a pluralistic and complex health care system. The higher purposes of education are served poorly when communities, usually poor, are exploited for 'teaching material' with a minimal return in continuing comprehensive health care."

In the Millis Commission Report one finds this statement: "The general practitioner leaves behind him a vacuum that organized medicine has not decided how to fill."

Answers to this and the other challenges to the medical profession, particularly medical education, may be found in the Willard Report, appropriately titled "Meeting the Challenge of Family Practice." Therein may be found a detailed description of how the ideal family physician of the future should function and the educational experiences that should prepare him for this field of practice.

It is generally conceded and is reflected in the above quotations that the emphasis of traditional medical education and training for all types of practice (including general practice) has been the episodic diagnosis and treatment of disease in seriously-ill hospitalized patients. In spite of this, many physicians of differing types and backgrounds provide their patients and families with personal, family-centered continuing comprehensive health services. However, they have had no special or specific training to function as family physicians and one might question their proficiency in this field. They have de-



veloped these attitudes, knowledge and skills through experience alone, without supervision, while in private practice, usually after many mistakes, occasionally tragic ones, in patient and family management.

As outlined in the Willard Report, the family practice training programs as now developing in a number of medical schools and other teaching hospitals are providing special and specific educational experiences to prepare residents to become superb family physicians. Through conducting a model of family practice under the supervision of experienced family physicians, behavioral scientists, consulting physicians, and allied health professionals, residents will not only learn the primary and continuing care of diseases (will learn especially how to treat common diseases uncommonly well) but will develop knowledge and skill in interpersonal communications, coordination of health services of all types, and definitive care of the very common emotion-induced illnesses. He will become people-oriented and develop healthy and strong physician-patient and physician-family relationships and will learn how these relationships make all of his care more effective.

The training programs are organized (institutionalized) and the team approach is stressed. By training family physicians, consulting physicians, and allied health personnel together, they will learn to work interdependently in the future comfortably, efficiently and effectively in providing comprehensive health services to people.

I'll conclude by asking several pertinent questions: How better can medical students learn about comprehensive health care than by participating in these training programs to an appropriate degree? Should not these family practice programs have strong support from the entire medical profession, including medical education and from all of society? What is more relevant for today and tomorrow in medical education?

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THE KEY TO THE success of any system of medical care is the participation of adequate numbers of physicians. The United States doesn't have enough physicians for present medical care needs, and the deficiency will amount to a disaster when the Medicare-Medicaid programs are expanded. Therefore, measures must be taken far beyond those presently being developed if the American people are to enjoy more than token nationwide health care.

Three measures presently in their developmental stages represent reasonable, and substantial, attempts to gear the medical machine for the enormous task ahead of it. Recruitment and training in the allied health professions will relieve physicians of many lesser tasks and free them to provide more physician attention. Group practice will increase their efficiency. Increased enrollment in medical school classes has already provided more doctors.

That such means for closing the physician-medical care gap are totally inadequate for the future is seen when one simply looks at the last of these—graduation of more physicians. In the past ten years medical school graduates in this nation each year are now increased by 25 percent. However, because of careers in research, administration and public health, the actual number of physicians available for patient care has decreased by 10 percent.

It is easy to suggest that in addition to larger medical school classes we simply make more medical schools. We have. From the base number left after the cleaning out of diploma mills that followed the Flexner report of 1910, the number has risen from 76 to 101. At \$100 million per

unit, however, this means of adding to the pool of physician medical care providers is fatally slow if enough physicians are to be available for the future.

So let us look in different directions and see if any other solutions to the dilemma can be generated.

We must remember we are up against time and money—two limitations which determine our choice of options. Therefore, if we can, we would like to modify an existing system to meet our needs.

We have just such a system in the existing undergraduate college structure. There is no reason whatever why the traditional first two years of medical school cannot be taught as the last two years of college.

The disadvantages of such a plan are few and are easily outweighed by the advantages. Tradition is practically the only stumbling block. It has always been thought that a student should come to medical school fully educated in the humanities with good grounding in science. This hope has seldom been realized and the student usually comes to medical school barely educated in the humanities with the conviction that that useless part of his life is behind him.

Eighteen to 20 year olds are far better suited to the pursuit of science courses, where didaction, memory exercises and base logic are all that is required, than they are to philosophy and history and poetry. The latter are better suited to the adult mind of 22 to 25 when it is confronted with the mystical issues of life, death, and disease. Tradition, therefore, can quite properly be reversed, and students can learn in their last two years of college, anatomy, physiology, biochemistry, bacteriology and even pathology. On the other hand, during their clinical years they can learn history, philosophy, geography, political science and other subjects which will educate them as advice-giving, mature physicians, while they are learning their clinical subjects.

This reversal of curriculum can do a great deal to multiply the options of the college student. At the end of his science education he can either go on to clinical medicine, or he can opt for a life of research, or he can choose to be a well qualified technician. Simple expansion of existing college courses can thus very inexpensively provide the first two years of medical school.

True, the Case-Western Reserve (and Rochester, Johns Hopkins and other) curriculae which bring the student into the clinical setting at the beginning of his experience will not be possible in the system suggested. However, the merits of these have yet to be proven, and they represent a luxury in holding down the number of physicians trained we can ill afford.

We must remember there are *twice* as many qualified students produced by colleges each year as are admitted to medical schools. We *must* utilize this existing resource. It doesn't matter too much if we have doctors trained clinically from their anatomy class years if we have half as many doctors as we need. The net quality of care is our concern, and to achieve a maximum quality for all the people we simply must have a significantly larger output of physicians.

Let us assume that the undergraduate colleges can indeed provide the basic science needs of the system of medical education. What will happen then? Just as we have the enormous, untapped, qualified pool of potential physicians and the extensive, effective, already constructed system of colleges and universities, we have the existing system of community hospitals already constructed and full of clinical material. That a significant number of these are quite adequate for the clinical training is attested by the use of them (including Veterans hospitals) for teaching by medical schools already.

Use of the clinical community hospitals for medical student training is simply an administrative matter. Construction of curriculae, proctoring of quality and all the other details which go into a proper medical education are well within the abilities of most Deans and Professors who are active today. True, the administrative procedure is bound to be somewhat more nebulous than where teaching is conducted amidst the bricks and mortar of the

ivy covered halls, but the difference is not insurmountable, and the difference in cost is unequivocal.

So, the whole system of medical education can be constructed from existing resources. The number of physicians trained can be doubled, the time required to achieve the structuring can be quite acceptable (and in time for the onslaught of need), and the cost can be held to a fraction of what it would be by simple expansion of our traditional system.

Before they crystallize, some objections which may come to the reader's mind should be discussed. First and foremost will be that this system will or may provide a second-rate medical education. There is nothing about it which indicates it *will* provide anything less than a first-rate education. All the necessities of preclinical and clinical training are provided. In addition, the student will have the opportunity to pursue his education in humanities as reading courses, seminars and lectures at a time in his life when he might just decide to continue to include them in his pursuits as a physician. That it *may* produce a second-rate education cannot be denied. So any educational pursuit can fail. Proper administrative control, however, can help guarantee a suitable outcome. The fears usually expressed stem mainly from 70 years ago, and it is hoped we can have learned something about maintaining quality of education since then.

Another objection is that the student may not have made up his mind as soon as his junior year in college. This is really no objection. When he does make up his mind he can start the program. Another objection is that there would be difficulty interdigitating the student in this program with existing programs. This is hardly so; he

would be qualified to start the third year at any other school, or if not the system would not be working properly.

One of the advantages of this system which does not accrue directly to this program to increase the numbers of physicians is the educational involvement of doctors in the community hospital, and another is the upgrading of care in the hospital.

Other side benefits can be included in this system. The student who wishes to pursue a research course can set out upon his career at the end of his college training and can achieve a Ph.D., for example, in hematology, as a member of the health team. When his special knowledge is needed in the care of a patient, say the drug treatment of leukemia or a bleeding disorder, there would be no duplication of physicians as there is now. Also, techniques for the development of a computer bank of specialized information will help the primary physician in his care and tend to reduce the fractionation of care and the duplication of physician talent which is now so wasteful of physician effort.

No departure from existing methods, such as is presented here, can come full formed, and, in addition to revamping the duplication of physician attention and the development of physician-memory banks many other innovations will be necessary to bring a solution to the problem of adequate medical care. Support for the development of such a system is needed now—and if it is successful it might just make the difference as to whether or not the government can make good on its inevitable promise to provide full medical care to the people.

# Important Advances in Clinical Medicine

## *Epitomes of Progress – Pediatrics*

*The Scientific Board of the California Medical Association presents the following inventory of items of progress in Pediatrics. Each item, in the judgment of a panel of knowledgeable physicians, has recently become reasonably firmly established, both as to scientific fact and important clinical significance. The items are presented in simple epitome and an authoritative reference, both to the item itself and to the subject as a whole is generally given for those who may be unfamiliar with a particular item. The purpose is to assist the busy practitioner, student, research worker or scholar to stay abreast of these items of progress in Pediatrics which have recently achieved a substantial degree of authoritative acceptance, whether in his own field of special interest or another.*

*The items of progress listed below were selected by the Advisory Panel to the Section on Pediatrics of the California Medical Association and the summaries were prepared under its direction.*

Reprint requests to: Division of Scientific and Educational Activities, 693 Sutter Street, San Francisco, Ca. 94102

### Rubella Vaccine

A live attenuated rubella vaccine is now available for general use. The currently proved facts about the vaccine are as follows: (1) no significant reactions have been associated with the use of the vaccine in children, (2) antibody responses occur in approximately 95 percent of recipients and the antibodies so engendered have not significantly declined over a three-year period, (3) although *vaccine virus* is shed in the pharynxes of recipients for as long as 40 days, it rarely spreads to susceptible contacts, (4) vaccine-induced antibodies protect against *disease*, (5) when challenged by natural rubella, *subclinical* reinfection of vaccinees occurs in approximately 30 percent of cases, (6) arthritis follows immunization in about 50 percent of females more than 20 years of age and, (7) the embryopathic potential of the

*vaccine virus* is not known. Because of this, the vaccine is contraindicated in pregnant women and vaccine administration to any post pubertal females must be approached with caution. At present the U.S. Public Health Service has recommended that children in kindergarten and the early grades of elementary school deserve initial priority for vaccination.\* Because of reinfection and the unknown embryopathic potential a vaccine surveillance system must be included in any vaccine program.

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\*Editor's note: A Joint Statement on Rubella Vaccine by the California Medical Association and the State Department of Public Health was published in the September, 1969, issue of *CMA News*.

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## Amniotic Fluid Analysis—A Cooperative And Multidiscipline Approach to the Prevention of Certain Inherited Disorders

By study of the amniotic fluid, it now appears possible to detect over 30 biochemical genetic disorders and a variety of chromosomal aberrations. Fluid usually is collected by amniocentesis sometime between the sixteenth and twentieth week of pregnancy. In experienced hands this procedure carries a very minimal risk for maternal or fetal complications.

The usual indications for such tests are those high-risk pregnant women who have already borne children with one of these specific disorders. The biochemical disorders are mostly rare, often serious, recessively inherited diseases. The most common heritable chromosome problem is the translocation-type Down's syndrome (mongolism).

An unfortunate drawback is the amount of time needed in most cases to do the analysis. For a few biochemical disorders the tests can be done directly on the fresh amniotic fluid specimen. In most biochemical cases, however, and for all chromosome studies the cells must be cultured four or more weeks. Barrbody prenatal sex determination can be done on the fresh specimen, and this sometimes is used to sharpen the risk calculation for certain serious, sex-linked, recessive diseases, for example hemophilia, pseudohypertrophic muscular dystrophy.

The obvious purpose for such prenatal detection is to reassure families when the specific diseases are absent and to alert them to abnormalities in sufficient time so that interruption of pregnancies is possible. Existing legislation in each state will determine the practicality of such diagnostic procedures.

Optimum utilization and progress in this relatively new field of preventive medicine require the combined efforts of competent obstetricians, clinical geneticist-counselors, advanced biochemical and chromosome laboratory facilities, public health support, scientific researchers and enlightened forward-looking legislation.

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## The Importance of Birthweight To Gestational Age

Over a decade ago, the term *low birth weight* was adopted internationally in preference to *prematurity*. Until then the term *prematurity* had described a mixture, from infants actually born prematurely to those full or even post-term.

True prematures are infants whose development in utero had progressed satisfactorily until the untimely early delivery of the infant. The premature infant, born too soon, is sized appropriately for the length of gestation.

All other infants of low birth weight have had an abnormal intrauterine growth for a variety of possible causes. They tend to be abnormally small for their gestational age. They include infants with chromosomal aberrations (Down's syndrome), genetic diseases (cystic fibrosis), metabolic diseases (osteogenesis imperfecta), maternal illnesses (toxemia), intrauterine infections (rubella) prolonged pregnancy (postmaturity) and congenital malformations (Potter's syndrome).

Newborns also can be excessively large for gestational age, as is seen in offspring of mothers with diabetes.

Mechanisms of smallness vary. Infants, for example, born after an intrauterine infection such as rubella, appear to have diminished numbers of cells.

Infants born to mothers with toxemia are examples of true intrauterine growth retardation, with normal numbers of cells but each cell apparently smaller than that of the normally sized infant for that gestational age.

Knowledge of appropriateness of size for gestation can provide important clues toward delineating diseases and also toward suggesting prognosis.

LOUIS GLUCK, M.D.

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## The Use of Clotting-Factor Concentrates for the Treatment of Hemophilia

Potent concentrates are now available for use in treating both factor VIII (antihemophilic factor) deficiency, classical hemophilia, and factor IX deficiency, Christmas disease. Cryoprecipitate prepared from single donor plasma is probably the most readily available and least expensive source of factor VIII; each bag of cryoprecipitate contains about 100 to 130 units of factor VIII activity (1 unit equals the activity in 1 ml of average fresh normal plasma). Factor VIII is also available as lyophilized cryoprecipitate (Courtland Antihemophilic Factor — about 250 units per 25 ml) and as a more potent concentrate made by Hyland (Hemophil®—about 250 units in 7 ml, also available in larger sizes).

Factor IX is present in whole plasma and is also available as a concentrate from Cutter (Konyne® — about 500 units in 25 ml). Proper use of concentrates for replacement therapy in hemophiliacs now makes surgical procedures much safer now than they were previously with only plasma.

CHARLES F. ABILDGAARD, M.D.

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## Recognition and Treatment Of Intravascular Coagulation

Disseminated intravascular coagulation (DIC) may be associated with a wide variety of diseases either as a complication or a pathogenetic mechanism. DIC may result in thrombotic complications due to widespread fibrin deposition or in hemorrhage due to consumption of coagulation factors, or in both. A number of rapidly available tests

are useful in recognizing the problem: platelet count, prothrombin time, partial thromboplastin time, fibrinogen screening test. Quantitative assays for fibrinogen, factor V, factor VIII are also helpful as is measurement of fibrinolysis and fibrin split products. Control of DIC by administration of heparin may be life-saving, but treatment of an underlying disease may be required for complete control. Examples of diseases that may be associated with DIC are: sepsis, burns, shock, metastatic malignancies, obstetrical complications, purpura fulminans, postoperative state (and many others).

CHARLES F. ABILDGAARD, M.D.

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## Current Immunization Procedures

The availability of new attenuated live virus vaccines has led to reexamination of immunization recommendations. In the first year of life DPT and polio immunization (given at the same time) are currently recommended. Vaccine for measles, mumps, smallpox and now rubella should not be given earlier than one year of age, both because of lower take rates and potentially higher adverse reactions. It is not clear whether or not boosters will be necessary for all of these live virus vaccines. Recent information indicates that tetanus antibody persists for a long time. Routine tetanus boosters are being given too frequently, and adverse reactions of hypersensitivity have been increasingly reported. The current recommendation for tetanus boosters after a primary series is every ten years. If a dose is administered as part of wound management, then the ten-year interval is determined from that date. The physician must remain flexible in his immunization recommendations to adapt to the new information concerning vaccine administration.

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## The Diagnostic Application Of Immunoglobulin Determinations

Immunoglobulin concentrations have been shown to be increased following antigenic stimulation of a fetus in utero as early as the twentieth week of gestation. With improved techniques in quantitation of immunoglobulins, it has now become feasible to employ determinations of IgM and IgA as a useful adjunct in the diagnosis of perinatal infection. With the chronic intrauterine forms of infection, most commonly caused by rubella and cytomegaloviruses, *Toxoplasma gondii* and *Treponema pallidum*, the elevated concentrations of IgM and IgA persist, even in the absence of symptoms, and can be demonstrated in cord sera collected from infected neonates.

Acute neonatal infections, caused by a variety of Gram-negative and Gram-positive bacteria and viruses, are followed by a sequential rise in immunoglobulins. Serial IgM and IgA determinations on sera collected from infants born with a history suggesting infection (i.e. prolonged rupture of amniotic membranes or maternal febrile illness) may be helpful in selecting acutely infected neonates from a group of infants with suggestive clinical findings. Even in the absence of symptoms, a concerted effort to define infection must be made in infants with elevated macroglobulin concentrations. Silent central nervous system and urinary tract infections can often be discovered.

Immunoglobulin determinations cannot be used to exclude infection but can be very helpful to select infants who are at risk for infection. When coupled with specific diagnostic techniques, including IgM fluorescent antibody methods, diagnosis can be achieved in the first few days of life.

Immunoglobulin deficiency states may be congenital or acquired and early detection of isolated or combined deficiencies of IgM, IgA or IgG is now possible with use of this quantitative approach.

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## Prevention of Erythroblastosis With Anti-Rh Gamma Globulin

Gamma globulin, prepared from high titer anti-Rh plasma, has proved to be highly effective in the prevention of primary immunization to the Rh<sub>0</sub>(D) factor. The treatment is given within 72 hours of delivery and is indicated in all Rh<sub>0</sub>(D) negative women who deliver an Rh positive infant and in whom at the time of delivery there has been *no* evidence of sensitization to Rh<sub>0</sub>(D). The preparation (RhoGAM,<sup>®</sup> Ortho Pharmaceutical) given in the dose of 1 ml, works by destroying Rh-positive fetal red cells which normally enter the maternal circulation at the time of delivery. This minor fetal-maternal bleed has been conclusively demonstrated to be the cause of primary anti-Rh stimulation in the mother. For continued prophylaxis throughout childbearing, therefore, treatment must be given at the termination of each pregnancy. In those instances where anti-Rh immunization is already established, the preparation has no value.

The immunogenic risk in pregnancies which terminate before term has not been ascertained; the problem is under investigation. Pending the outcome of these investigations, however, it is considered advisable to administer the preparation to all Rh-negative women who have therapeutic abortions as well as those who after the first trimester deliver an infant of unknown or of Rh-positive type.

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## Intensive Care Nursery

Techniques for intensive care have been adapted to the requirements of the newborn infant. It is now possible to monitor simultaneously heart rate, respiratory rate, arterial and venous blood pressure, electrocardiogram, ambient oxygen and temperature. Improved micro laboratory techniques have made repetitive study of blood gases and acid-base balance possible even in small premature infants. Assisted ventilation can be maintained for long periods if necessary. Clinical application of these techniques requires specially trained physicians and nursing personnel. The ratio of staff to infants must be one to two, three or four. Intensive care has improved mortality from asphyxia, congenital heart disease and neonatal operations, but its place in the treatment of respiratory distress syndrome has not been definitely established.

JOAN E. HODGMAN, M.D.

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## Phototherapy in the Treatment Of Hyperbilirubinemia

Phototherapy is an effective treatment for hyperbilirubinemia of non-hemolytic origin. When premature infants are kept under a bank of fluorescent lights from the first day of life onward, the serum bilirubin levels are lower on day 4 than in infants not receiving this therapy. The need for exchange transfusions is reduced and fewer infants get into the area of moderate hyperbilirubinemia where a danger of subtle brain damage may exist. Since the site of action is in the skin, the yellow color sometimes disappears and it becomes more difficult to estimate serum bilirubin level from clinical appearance. Loose green stools sometimes occur but weight loss and dehydration are not ap-

parent. A slate-gray skin color is sometimes seen but this appearance is not associated with any recognized toxic effect. While a number of theoretical hazards of phototherapy have been proposed, no toxicity has so far been documented.

The major value of phototherapy is in the small, critically ill or bruised premature in whom moderate hyperbilirubinemia is undesirable and exchange transfusion hazardous. The value of phototherapy in the treatment of erythroblastosis due to Rh incompatibility or in other hemolytic processes in which the rate of rise of serum bilirubin is rapid has yet to be evaluated.

BRUCE D. ACKERMAN, M.D.

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## Gentamicin in the Treatment Of Gram-Negative Infections

Gentamicin sulfate (Garamycin®, Schering) is a new broad-spectrum antibiotic related to streptomycin, neomycin, paromomycin and kanamycin. It is available as a cream or ointment for local use on the skin and also for intramuscular injection.

Gentamicin is bacteriocidal *in vitro* against *Staphylococcus aureus* including strains resistant to penicillin-G, and also against many strains of *Pseudomonas aeruginosa*, *E. coli*, *Klebsiella-Aerobacter* species and proteus. In general, when organisms acquire resistance to gentamicin they have also acquired resistance to streptomycin, neomycin, paromomycin and kanamycin. However, some strains resistant to others in the group may still be sensitive to gentamicin.

The unique contribution of gentamicin is in its effect upon pseudomonas. Against this organism the other agents mentioned are relatively ineffective and gentamicin approaches the activity of the polymyxins.

Nephrotoxicity and ototoxicity, especially affecting the vestibular systems, are significant, and the ototoxicity may be permanent. Toxicity is closely related to blood levels of 10 µg per ml or higher. Blood levels in turn are related primarily to dosage and to renal function.

The entire April-May, 1969, issue of *The Journal of Infectious Diseases* is devoted to this subject and is recommended for detailed information.

BENJAMIN M. KAGAN, M.D.

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### Zoster Immune Globulin For Chickenpox Prevention

Zoster immune globulin (ZIG) is effective in preventing chickenpox when given to children within 72 hours of exposure. The minimum effective dose has not been established; however, 2 ml of 16.5 percent gamma globulin prepared from patients with high varicella-zoster complement fixing antibodies provides adequate prophylaxis. Immune serum globulin appears to be ineffective in prevention but may modify the disease when large amounts are used. Since chickenpox is generally a benign disease, passive immunization with ZIG should be limited to patients at high risk, such as children receiving steroids or immunosuppressive drugs, newborn infants, and children with debilitating diseases, particularly malignant disease.

RICHARD L. TOMPKINS, M.D.

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Ross AH: Modification of chicken pox in family contacts by administration of gamma globulin. *New Eng J Med* 267:369-376, 1962

### The Hemagglutination Inhibition (HI) Antibody Test for the Determination Of Immunity to Rubella

The HI test, when properly done, is an excellent, rapid, inexpensive method for determining the rubella immune status of an individual. The accurate determination of rubella HI antibodies is especially pertinent as current recommendations suggest that if vaccination of a woman of childbearing age is contemplated, she should be tested for ru-

bella HI antibody. If such antibodies are present, nothing can be gained by immunization. If the test is performed by competent technologists, the presence of any level of HI antibody can be considered indicative of previous infection. If a physician requires aid in the interpretation of test results, his local health department can provide it. Not all the kits available commercially yield reproducible HI results in the hands of the personnel of the average hospital laboratory. Training programs for technologists are currently being sponsored by the State of California Department of Public Health and local medical schools.

BERNARD PORTNOY, M.D.

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### Diagnosis of Rubella

The hemagglutination-inhibition test as a diagnostic aid has been generally available in laboratories for some time. However, several studies have shown that considerable care must be exercised in interpreting the results. Both false positive and negative tests can be reported because of the difficulties associated with the removal from the serum of non-specific inhibitors of the hemagglutination reaction. If doubt persists, the use of tissue culture neutralization plus complement-fixation tests should resolve the problem.

J. J. QUILLIGAN, JR., M.D.

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## Availability of Improved Centers for the Diagnosis and Treatment of Children With Congenital Defects, Learning And Neurological Disorders

Dramatic rescue of the fetus or neonate from death is not enough. The child who survives a stormy prenatal or neonatal period requires skilled diagnosis and sensitive treatment of congenital defects (including subtle aberrations of learning capabilities) if crippling consequences are to be avoided.

Centers utilizing interdisciplinary concepts of diagnosis, counsel and remediation are demonstrating the value of the truly synergistic approach. Problems posed by multiple handicaps (genetic, metabolic, post-infectious, post-traumatic) as well as variations in family understanding, and different (often ingenious) reactions of adaptation in the child — are but a few of the factors which demand attention.

Appropriate use of centers may make the difference between mere survival and zestful development of full potential for many children.

MAXINE M. SEHRING, M.D.

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- Management of the child with learning disabilities: An interdisciplinary challenge. *Reports of Annual Conferences of Association for Children with Learning Disabilities* (1967, New York; 1969, Texas), 2200 Brownsville Road, Pittsburgh, Penn 15210

## Recognition and Treatment Of Heart Disease in the Neonate

It has been estimated that almost one out of every 100 infants will be born with a congenital cardiac abnormality. Of this group as many as 50 percent may have died by one month, most of

them in the first week of life. The lives of many of these infants can be salvaged by early diagnosis and skilled management. Therefore:

- There must be a high index of suspicion for the presence of a cardiac defect in an infant "not doing well."
- It must be recognized that signs of cardiac abnormalities in the neonate may be obscure and atypical.
- The murmur as an indication of a cardiac abnormality may not, and usually is not, present in the neonate with the more severe type of cardiac lesion, such as transposition of the great vessels or pulmonary atresia—the very lesions which require early diagnosis and surgical intervention.
- Common and curable cardiac abnormalities including patent ductus arteriosus and ventricular septal defect may present in early infancy as severe congestive failure and lead to death unless proper medical or surgical measures are immediately undertaken.
- Because the symptoms and signs of a cardiac abnormality are difficult to assess clinically, the sick infant must be evaluated in an institution which not only has facilities and skilled personnel for cardiac catheterizations and angiograms, but also an arrangement for an immediate and smooth transition from the diagnostic to the surgical amphitheatre for infants in whom an operable cardiac abnormality is detected.

• There are many procedures now available which will keep the neonate alive until a correctable surgical procedure can be performed. These include a balloon septostomy (Rashkind) for the transposition of the great vessels, total anomalous venous return, mitral atresia or tricuspid atresia, which can be performed at the time of the diagnostic procedure, and palliative procedures such as banding of the pulmonary artery to decrease pulmonary blood flow or a variety of shunt procedures to create or increase blood flow to the lungs.

SAUL J. ROBINSON, M.D.

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## Child-Resistant Containers

Poisons kill about 500 children a year. Public education programs have failed to reduce the mortality and morbidity of ingestions. Preventing access to medicines and household products by the child is effective.

"Palm-N'-Turn" safety caps, which require pressure and turning to open, cannot be removed by children under four years old. Use of them does not increase cost of containers now being used for solids and liquids. Legislation requiring safety caps on containers of medications and toxic household items has been introduced into Congress.

KATHLEEN C. MORTON, M.D., F.A.A.P.

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## Slow Virus Infections

About 15 years ago, Sigurdsson proposed the idea of "slow infections" in sheep in Iceland. A progressive pathological process was caused by agents which had a long incubation period of months or years. In the past five years Gajdusek and Gibbs have produced clear evidence that certain chronic neurologic diseases are slowly progressive viral infections. "Scrapie" in sheep may appear three or four years after inoculation, and in "Kuru" in human beings it may be even longer before a neurological illness is evident. Dawson's "inclusion encephalitis" recently has been shown to be caused by the measles virus; this devastating neurologic syndrome occurs months or years following the initial childhood measles.

The hallmarks of measles virus — cytoplasmic and nuclear inclusion bodies and multinucleated giant cells — have been found in all forms of measles encephalitis from acute toxic to sequelar forms in which death occurs years later. Measles antibodies have been demonstrated in increased amounts in patients with multiple sclerosis (MS) as compared with control subjects; and similar pathologic findings in some patients with MS sug-

gest that the measles virus may be a slow or persistent viral infection related *in some way* to this tragic neurological disease.

JOHN M. ADAMS, M.D.

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## Undernutrition and Child Development

For a number of years evidence has been accumulating indicating that the growing child is particularly vulnerable to undernutrition. This peculiar vulnerability is perhaps best described as a curtailment in a number of factors of growth and development which may be permanent even if the child is subsequently rehabilitated. Severe undernutrition during the first year of life (infantile marasmus) will permanently stunt growth, prevent the normal increase in head circumference, retard bone age and slow down the rate of cell division and myelin synthesis in brain. Data from a number of widely varying sources also strongly suggest that children who have survived a period of severe malnutrition early in infancy are retarded in their development. Permanent deficits in perceptual development and cognitive function have been described in these infants. These deficits remained even after long periods of rehabilitation. Studies are in progress to determine exactly the severity and duration of undernutrition that is necessary to produce these effects.

MYRON WINICK, M.D.

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## Valium in the Treatment of Epilepsy

Diazepam (Valium®), a tranquilizer-muscle relaxant in the same family with Librium® and Magodon®, has proved very valuable in the treatment of status epilepticus. Many neurologists con-

sider it the drug of choice, now to be used in preference to paraldehyde, especially in children. For severe and intractable seizures, intravenous slow drip of 100 mg and 500 ml of normal saline solution is recommended with the total dose initially being 10 to 15 mg per square meter of body surface. The most significant side effects are moderate hypotension and mild respiratory depression, both most commonly seen in adults and in conjunction with barbiturates or paraldehyde. Diazepam has also proved useful as an oral adjunct with other drugs in the long-term control of convulsive disorders.

TOM W. ROBINSON, M.D.

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### Growth Retardation in Environmental Deprivation

Environmental deprivation is perhaps the most frequent cause of growth failure in infancy. In older children it is less frequent as a cause of growth failure. If careful history taking, careful physical examination and simple laboratory testing (blood cell count, urinalysis, serum urea, protein-bound iodine) fail to reveal an organic cause, environmental deprivation should be considered. Infants with mental retardation may not grow adequately whether they are deprived or not. Admission to a hospital may be necessary to determine if an infant can gain weight if adequately nourished and cared for. Testing should be held to a minimum during this time.

S. A. KAPLAN, M.D.

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### Intravenous Alimentation

Nearly complete alimentation can now be accomplished intravenously for long periods of time. This technique requires the placement of a silastic or polyvinyl catheter into the right atrium via the jugular, subclavian or femoral veins. In the right atrium, the large volume of blood flow will immediately dilute the hyperosmolar solution of 25 percent glucose, 4 percent fibrin hydrolysate, required electrolytes and vitamins. The volume of infusion is equivalent to the maintenance water requirements and should be given at a constant rate with a pump. The maximum rate of glucose utilization is 1.3 grams per kilogram of body weight per hour. A Millipore filter in the line will remove particulate matter and microorganisms. Essential fatty acids and trace metals are supplied by transfusion of plasma twice weekly. Improved survival has occurred in patients who are unable to eat because of prolonged ileus, chronic diarrhea, intestinal fistulae, peritonitis and sepsis. Complications include septicemia (particularly *Candida*), venous thrombosis and, rarely, pulmonary embolism. This technique of parenteral alimentation is one of the most important medical advances in many years.

ALFRED A. DELORIMIER, M.D.

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### Drug Abuse

The most common mind-altering substances being abused by youth today are the hallucinogens, amphetamines and barbiturates. The hallucinogenic substances hemp (or marijuana), lysergic acid diethylamide (LSD), peyote, and mescaline all produce acute panic reactions, recurrent hallucinations, and serious psychotic change with varying frequency, but most commonly with LSD. Such untoward reactions with marijuana use are more rare due to the low content of the active

ingredient, tetrahydrocannabinol, in the material most commonly available. Methamphetamine, because of the rapidity with which dependence and tolerance develops and because abuse produces a chronic brain syndrome, is certainly the most dangerous drug being abused by young people. The oral use of dextroamphetamine, which is more common in high schools, is often followed by a shift to methamphetamine. Barbiturate use is also

common in the high school ages and represents an introductory move toward further experimentation with chemical solutions for life's problems.

HENRY B. BRUYN, M.D.

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## ADVISORY PANEL SECTION ON PEDIATRICS

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In addition, the following physicians met with the panel and participated in the selection and preparation of these epitomes: GLENN E. AUSTIN, M.D., *American Academy of Pediatrics, Council on Pediatric Practice, Los Altos*; LEO S. BELL, M.D., *American Academy of Pediatrics, Council on Pediatric Practice, San Mateo*; JOHN A. BISHOP, M.D., *American Academy of Pediatrics, Chairman, Chapter 3, San Diego*; WILLIAM MCCLELLAND BROWNLEE, M.D., *American Academy of Pediatrics, Treasurer, Chapter 3, San Diego*; RALPH W. COFFELT, M.D., *American Academy of Pediatrics, Immediate Past President, District 9, Burbank*; CARL W. ERICSON, M.D., *American Academy of Pediatrics, Pasadena*; BURTON FINK, M.D., *President, Los Angeles County Pediatric Society*; BIRT HARVEY, M.D., *American Academy of Pediatrics, Alternate Chairman, Chapter 1, Palo Alto*; ROBERT J. HARVEY, M.D., *CMA Section on Pediatrics, Immediate Past Chairman, San Francisco*; ALEXANDER HATOFF, M.D., *American Academy of Pediatrics, Chairman, Chapter 1, Oakland*; H. JAMES HOLROYD, M.D., *American Academy of Pediatrics, Secretary-Treasurer, Chapter 2, La Canada*; IAN BRUCE JOHNSTON, M.D., *American Academy of Pediatrics, Immediate Past Chairman, Chapter 1, Walnut Creek*; FREMONT P. KOCH, M.D., *American Academy of Pediatrics, Chairman, Chapter 2, Arcadia*; VICTOR Y. LINDBLADE, M.D., *American Academy of Pediatrics, Alternate Chairman, Chapter 3, San Diego*; WILLIAM D. MISBACH, M.D., *American Academy of Pediatrics, Alternate Chairman, Chapter 2, Encino*; EDWARD J. OTTENHEIMER, M.D., *American Academy of Pediatrics, Secretary, Chapter 3, San Diego*; TOM W. ROBINSON, M.D., *CMA Committee on School and College Health, Chairman, Newport Beach*; MELVIN H. SCHWARTZ, M.D., *American Academy of Pediatrics, Secretary, Chapter 1, Alameda*; MAXINE SEHRING, M.D., *School Health Committee, American Academy of Pediatrics, Walnut Creek*; EDWARD B. SHAW, M.D., *University of California, San Francisco Medical Center*; LOUISE YEAZELL, M.D., *American Academy of Pediatrics, Treasurer, Chapter 1, San Francisco*.



## MEDICAL STAFF CONFERENCE

# Differential Diagnosis of Platelet Dysfunction

*These discussions are selected from the weekly staff conferences in the Department of Medicine, University of California at San Francisco. Taken from transcriptions, they are prepared by Drs. Martin J. Cline and Hibbard E. Williams, Associate Professors of Medicine, under the direction of Dr. Lloyd H. Smith, Jr., Professor of Medicine and Chairman of the Department of Medicine.*

DR. SCHMID:\* Dr. Schambelan will give the case presentation this morning.

DR. SCHAMBELAN:† This patient was a 15-year-old, white male. He was transferred to this hospital from Oroville Medical Center Hospital on 6 June 1969 and died on 9 June. The medical history was of approximately one month's duration. In early May 1969, he complained of tiring easily and of vague, left upper quadrant pain. At the end of May he noted bleeding gums, which were treated with penicillin. Within the next few days he complained of generalized weakness, and a temperature in the range of 101 to 102°F was noted. The day before entering Oroville Hospital, he vomited blood and black material.

At Oroville Hospital he continued to have a temperature of 101°F accompanying a widespread, petechial rash and splenomegaly. Laboratory studies included a hemoglobin of 15 grams per 100 ml and a white cell count of 20,800 per cu mm, with 60 percent of the cells described as atypical lymphocytes. Platelets were not counted but described as "adequate on the smear." A monospot test was negative. The serum uric acid was above the upper limits of the scale (12 mg per 100 ml). Because of continued gastrointes-

tinal bleeding and a falling hematocrit and platelet count, the patient was transferred to this hospital.

On physical examination the blood pressure was 140/50 mm of mercury. The patient had tachycardia and was normothermic. He was frightened and pale, and appeared acutely ill. Petechiae were present over the entire body. The gums were hypertrophied and bleeding. The spleen was felt five fingerbreadths below the left costal margin. Neurological examination was significant for moderate weakness of the left lower extremity with an upgoing toe on that side. Ptosis and sixth nerve palsy were noted on the left side.

Initial laboratory data included hemoglobin of 10.6 grams per 100 ml, hematocrit of 31 percent, and platelet count of 52,000 per cu mm. White cell count was 23,300 per cu mm. The peripheral smear showed 31 percent of the cells to be mature lymphocytes and 20 percent lymphoblasts. Urine obtained by catheterization showed 2+ protein and a few coarse, granular casts. No cellular elements were present. Mild hyponatremia was present. Potassium content was 6.0 mEq, carbon dioxide 18 mEq, and chloride 80 mEq per liter. Creatinine was 8.5 mg and the serum uric acid 54 mg per 100 ml. Prothrombin time was 14.6 seconds, and partial thromboplastin time was estimated at 83 seconds. Fibrinogen was 460 mg per 100 ml.

\*Rudi Schmid, M.D., Ph.D., Professor of Medicine.

†Morris Schambelan, M.D., Resident in Medicine.

Initial x-ray films of the chest were considered normal; however, a later film showed right upper lobe collapse. The electrocardiogram was unremarkable. The bone marrow showed acute lymphoblastic leukemia.

The patient's course was very hectic. The first night in the hospital he was given fluids, whole blood, platelet transfusions, alkali for the metabolic acidosis, and allopurinol. He remained anuric during the first eight to ten hours despite central venous pressure within the normal range. Considered in differential diagnosis as to the cause of the anuria were tubular necrosis, gouty nephropathy, and leukemic infiltration of the kidneys. A renal scan performed at midnight on the day of admission showed slow accumulation of dye bilaterally and no evidence of infiltrates in the kidney. That same night a Scribner shunt was inserted. The patient was dialyzed the following morning and again the following day, and a modest reduction in the uric acid level was achieved. Once dialysis was under way, prednisone, vincristine, cephalothin (Keflin®), and kanamycin were given. A rapid fall in the leukocyte and platelet counts occurred over the next two days. On 8 June the patient became hypotensive and comatose. There was no recordable central venous pressure. The blood volume was expanded with fluids and he was given platelets and isoproterenol (Isuprel®). He responded briefly but died the following day.

The findings at postmortem examination included evidence of gouty nephropathy and rupture of the spleen. The latter probably caused his death.

DR. SCHMID: This patient presents a number of points for discussion. The treatment of acute leukemia is certainly one aspect. Another important point is the striking hyperuricemia — one of the highest values I have ever seen. However, we have chosen today to concentrate on the problem of platelet dysfunction and have asked Dr. Mervyn Sahud to be our discussant. Dr. Sahud is a Research Fellow with Dr. Aggeler and Dr. Wallerstein.

DR. SAHUD:\* In the case just presented, it should be emphasized that a platelet count of 140,000 per cu mm was recorded on 4 June, at a time when the patient was having rather profound mucocutaneous bleeding. In the association of non-thrombocytopenic bleeding with normal clotting

time, normal clot retraction and no evidence of accelerated clot lysis, there are still several possibilities in the differential diagnosis of bleeding:

- The patient could have had mild von Willebrand's disease. With a modest depression in Factor VIII level, the partial thromboplastin time would not be prolonged. The lack of history of previous bleeding, however, makes this diagnosis unlikely.

- The acute defibrination syndrome also had to be considered. This condition has been studied in acute promyelocytic leukemia,<sup>1</sup> but not in leukemia of other cell types. When high levels of early fibrin-split products are present (especially the large, early fractions), two defects in hemostasis may occur: (1) defective platelet clumping and (2) defective fibrin polymerization. However, this condition can be excluded in the present case because of the normal Quick and partial thromboplastin times, the high fibrinogen level, the near normal platelet count, and the absence of accelerated clot lysis.

- Another theoretical cause of bleeding in disease of this type is extreme leukocytosis (levels greater than 150,000 per cu mm). Harrison and coworkers<sup>2</sup> have shown *in vitro* inhibition of adenosine diphosphate (ADP)-induced platelet aggregation by leukocyte-rich, platelet-rich plasma. In the case here presented, however, the white cell count never rose above 20,000 to 30,000 per cu mm.

- The problem of platelet dysfunction associated with hyperuricemia was considered. However, so far as I know no one has ever described a relationship between the hyperuricemia and defective platelet plug formation.

- Eliminating all of the foregoing possibilities, the bleeding diathesis in this case could very well have been because of a disorder of intrinsic platelet function. More specifically, this condition could have been a disorder of defective platelet-collagen interaction with resultant impairment of platelet ADP release. Such a disorder can cause serious mucocutaneous bleeding and has recently been described in a patient with acute myeloblastic leukemia.<sup>3</sup> It is this intrinsic type of platelet disorder that we have been studying and which I will discuss today.

Disorders of platelet function may be classified as primary or secondary (Table 1). Notice that von Willebrand's disease is not part of this list

\*Mervyn A. Sahud, M.D., Research Fellow in Medicine.

TABLE 1.—Platelet Functional Disorders

Primary Type
Glanzmann's disease (Essential thrombasthenia)
Primary platelet dysfunction (Defective platelet-collagen interaction)
Macrothrombopathia
Scurvy
Miscellaneous examples
Acute leukemia
Wiskott-Aldrich syndrome
Polycythemia vera
Secondary Type
Uremia
Hyperviscosity syndrome
Drug-induced

because it is considered a disorder resulting from the lack of a plasma factor which is yet unidentified. The primary platelet disorders may be treated with platelet transfusions when clinically indicated. The secondary disorders have in common reversibility of the defect with improvement of the underlying disease state.

Before discussing these disorders further, I will discuss some biochemical aspects of primary hemostasis which have recently come into focus. Because of advances in biochemistry and electron-microscopy, what appeared initially to be a rather uncomplicated event has become incredibly complex. In the field of primary hemostasis, the most important biochemical discovery of the last decade was the identification in 1961 by Gaarder and coworkers<sup>4</sup> of ADP as a naturally occurring, potent, platelet-aggregating agent. Before that time, Born<sup>5</sup> had observed a rise in the phosphorus content of platelet-rich plasma after the addition of thrombin. It was not difficult to predict that platelets would be shown to have very high quantities of ADP and adenosine triphosphate (ATP). Recently, it has been demonstrated that platelets contain two pools of ADP, one of which is metabolically inactive and primarily available for release. The concentration of ATP in platelets is higher than in any other mammalian tissue, except for striated muscle and adrenal medulla tissues. The specificity of ADP for effecting platelet aggregation is unique, although a synthetic compound, 2-chloroadenosine diphosphate (roughly tenfold more powerful than ADP), and a natural compound, guanosine diphosphate (one-fiftieth as powerful as ADP), are also effective. Moreover, the ratio of ATP to ADP in platelets is only 2:1, emphasizing the high degree of specificity of ADP for platelets. (In striated

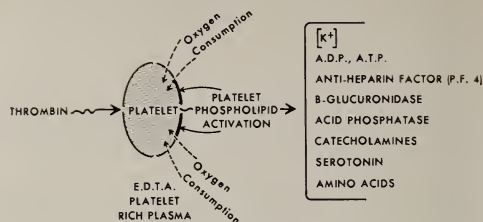
BIOCHEMICAL COUNTERPART  
OF VISCOUS METAMORPHOSIS

Chart 1.—Biochemical counterpart of viscous metamorphosis.

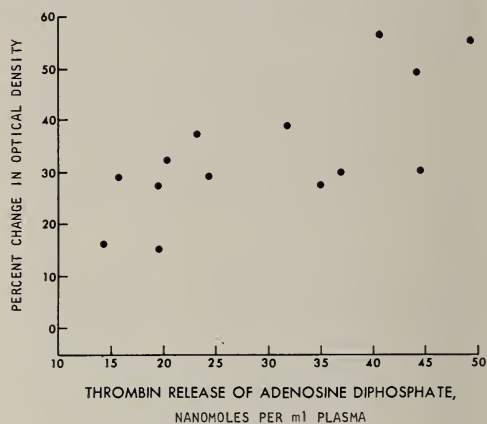


Chart 2.—Thrombin, 0.1 units per ml (final concentration), added to each subject's (1) EDTA, platelet-rich plasma for measurement of nucleotide release and (2) citrated, platelet-rich plasma for measurement of degree of platelet aggregation. Published with permission of the Society for Experimental Biology and Medicine. The chart is a part of "Utilization of ascorbic acid during platelet aggregation," by Sahud MA, and Aggeler PM (in press).

muscle and red blood cells, the ratio of ATP to ADP is 11:1 and 9:1, respectively.)

In 1962 Grette<sup>6</sup> showed that ADP is released by platelets when thrombin is added to platelet-rich plasma. This fact established the platelet as a secretory cell having a mode of operation similar to cells of the adrenal medulla. The so-called release reaction is what might be termed the biochemical counterpart of viscous metamorphosis (Chart 1). All the biologically active agents are released independently of platelet aggregation in ethylene-diaminetetraacetic acid (EDTA), platelet-rich plasma after the addition of thrombin. In addition, oxygen is actively consumed and platelet phospholipid becomes activated on the membrane. Our own observations regarding the release of





Figure 1.—Normal resting platelet, glutaraldehyde fixation, magnified approximately 32,000 times.

ADP after the addition of thrombin to platelet-rich plasma (Chart 2) show a direct correlation between degree of platelet aggregation (identified as the percent change in optical density) and the release of ADP in the plasma.

The next significant historical finding was the specific adhesion of platelets to subendothelial collagen<sup>7</sup> (not to elastin or endothelial basement membrane) and the subsequent release of ADP<sup>8</sup> from platelets in a magnitude similar to that produced by thrombin. Finally the discovery by Bettex-Galland and Lüscher<sup>9</sup> of a contractile protein with adenosine triphosphatase activity in platelets was a further contribution to our understanding of platelet biochemistry. This discovery gave support to the concepts that platelets are directly involved in clot retraction and that they may also be involved in aerobic metabolism as well as glycolysis.

Electron microscopy of the normal resting plate-

let (Figure 1) has helped clarify many aspects of platelet function. This particular platelet was processed by courtesy of Dr. Donald MacKay of the San Francisco General Hospital. The dense bodies (arrow 3a) have been called alpha hyalomer and appear to contain high concentrations of serotonin as well as the stored forms of ADP and ATP, which are secreted during the release reaction. After the addition of agents such as thrombin or collagen to platelet-rich plasma, these dense bodies aggregate centrally and subsequently disappear as nucleotides and serotonin are released into the environment.<sup>6</sup> The other dark, dense bodies (arrow 3b) are glycogen granules and are important because they represent the major source of platelet metabolism. On this particular section, mitochondria are not clearly visualized, but they do exist and are responsible for a lesser fraction of oxidative respiration. The small, complex vesicular network (arrow 3c) represents endo-

plasmic reticulum. Small microtubules exist at the outer edge, near the plasma membrane (arrow 3d), and are thought to contain thrombasthenin (determined immunologically).<sup>10</sup> Zucker-Franklin and coworkers<sup>11</sup> have postulated that microtubules may depolymerize to form microfibrils during cooling of the platelets and that this process may be reversed when platelets are rewarmed. There is some evidence that a relationship exists between the contraction phase (discoid form) and relaxation phase (spheroid form) of the platelet and the thrombasthenin-containing, microfibrillar structures.

Figure 2 represents the electron microscopic evidence of viscous metamorphosis, sometimes referred to as thrombocytorrhexis.<sup>13</sup> The reactions which culminate in this advanced degree of platelet plug formation may be summarized as follows: (1) There is injury to a vessel wall with attraction of circulating platelets to exposed subendothelial collagen (most specifically because of the terminal epsilon-amino groups of lysine on the collagen fibril).<sup>14</sup> (2) After a short incubation period, ADP is released from these adherent platelets with resultant cohesion of many platelets into a platelet mass. (3) Simultaneously, exposure of collagen to the plasma activates Hageman factor (Factor XII). (4) Also, platelet factor 3 is activated during the release of ADP so that the generation of thrombin is hastened. (5) Small amounts of thrombin (even concentrations below that which effect fibrin formation) produce more ADP release from locally stagnated platelets and thus increase the platelet mass even further. (6) Ultimately, the platelet plug is rendered impermeable as fibrin forms around it. (7) Retraction occurs within the plug as a result of thrombasthenin, the platelet contractile factor.

Disorders of platelet function have now been studied *in vitro* using platelet aggregometric techniques, which have helped clarify the mechanism of these diseases. In essential thrombasthenia (Glanzmann's disease), a rare congenital bleeding disorder, the principal defect is absence or pronounced impairment of clot retraction. Since the amount of platelet contractile factor (thrombasthenin) in these platelets is normal, a qualitative disturbance of this protein may be present. The clot retraction is improved by magnesium or fresh platelets. In addition, the bleeding time is prolonged, glass bead platelet adhesiveness is defective, and the platelets do not aggregate with

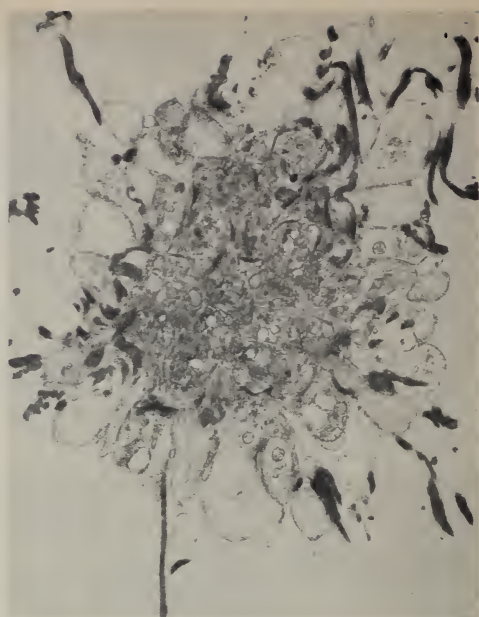


Figure 2.— Stage of thrombocytorrhexis. (Reprinted with permission of Dr. N. Rodman.<sup>12</sup>)

ADP, even in high concentrations. Likewise these platelets do not aggregate with either epinephrine or collagen. Only antiplatelet antisera has been shown to aggregate these platelets. The concentrations of ATP and ADP in these platelets are normal, and their ability to release nucleotides and serotonin is likewise normal.

In the normal aggregometric tracing (Chart 3), using the method of Born,<sup>15</sup> a decrease in optical density reflects the clumping of continuously stirred platelets in citrated, platelet-rich plasma at 37°C. The ordinate represents the percent of change in optical density. A small concentration of ADP (Chart 3a) causes immediate aggregation. After a temporary lag phase, a rapid release of intrinsic ADP occurs, forming the second wave of aggregation. With a higher concentration of ADP (Chart 3b) this secondary wave is obscured. With a collagen suspension, the aggregation is preceded by an incubation period of about a minute, during which time a slight increase in optical density occurs (Chart 3c). This increase is probably related to a change in platelet shape from discoid to spheroid form. The release of platelet ADP is sudden and results in rapid platelet clumping. Epi-



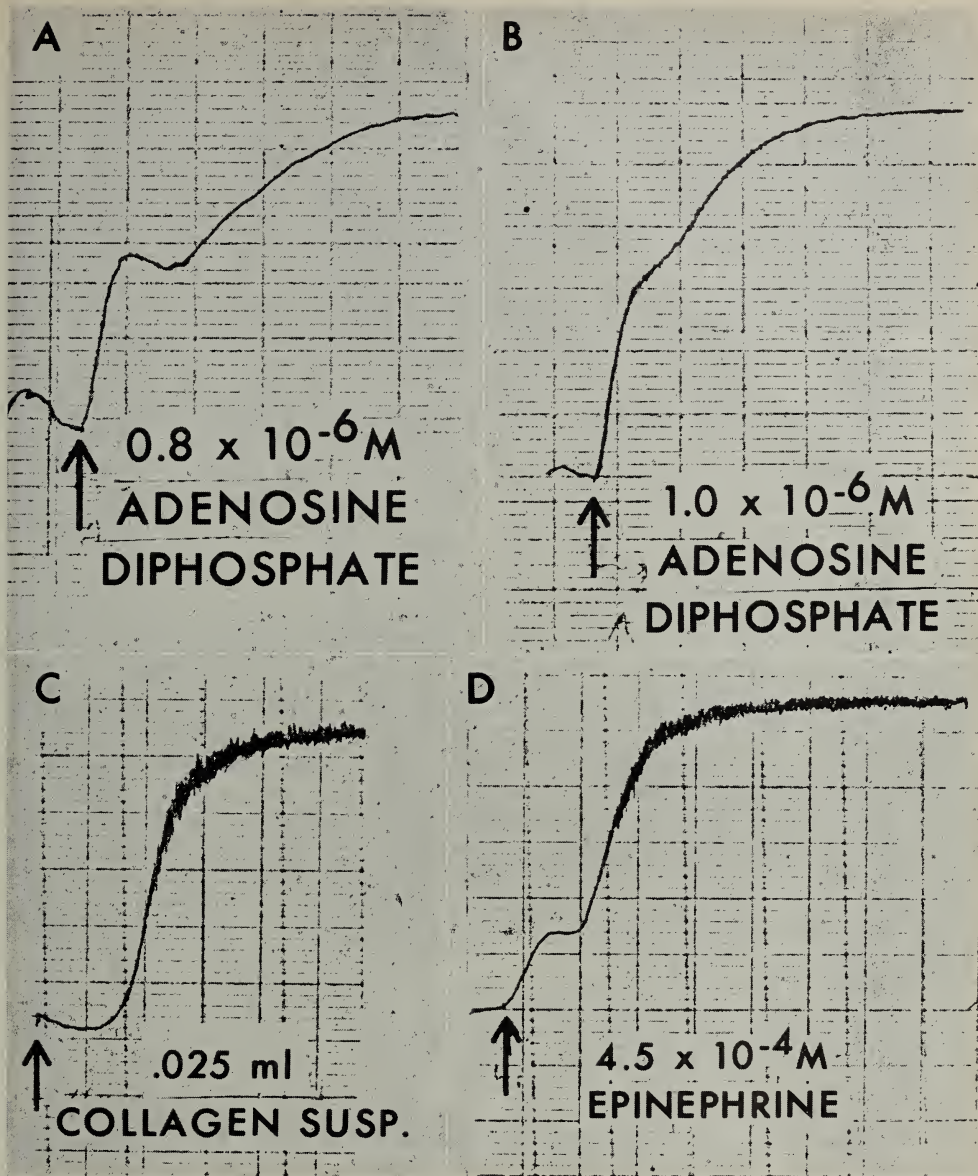


Chart 3.—Normal platelet aggregation as studied in citrated, platelet-rich plasma at  $37^{\circ} \text{ C}$  after the addition of ADP, collagen suspension, and epinephrine.

nephrine (Chart 3d) produces an initial phase of aggregation followed by a lag phase, after which time intrinsic release of ADP again occurs abruptly.

Primary platelet dysfunction is a distinct bleeding disorder, although milder than essential throm-

basthenia. Clot retraction, Factor VIII levels, and platelet counts are normal, but glass bead platelet adhesiveness is impaired and bleeding time is prolonged. Availability of platelet factor 3 is variable. This disorder (Table 2) may be familial. It occurs



TABLE 2.—*Features of Bleeding Syndrome Associated with Defective Platelet-Collagen Interaction*

Bleeding history
Mainly mucocutaneous
Probably familial
Occurs in males and females
Prolonged Ivy bleeding time
Profuse bleeding noted in 3 of 4 cases
Platelet aggregation with
ADP: Normal (but rapid disaggregation occurs)
Thrombin: Normal
Collagen: Absent
Epinephrine: Absent or blunted
Variable platelet factor 3 availability
Normal platelet count, factor VIII level, clot retraction
Defective nucleotide release after collagen exposure
Defective Salzman glass bead adhesiveness (pronounced)
Defective platelet-collagen adhesion under phase microscopy

in males or females at any age. Caen and coworkers<sup>16</sup> have reported two families with a similar mild bleeding disorder, and we have found a mother and daughter with this problem.

The most striking platelet abnormalities are found by use of the platelet aggregometer (Chart 4). With low concentrations of ADP (Chart 4a), normal aggregation is followed by premature disaggregation. With epinephrine (Chart 4b), the first wave of aggregation is either absent or blunted and no second wave of aggregation occurs. With thrombin (Chart 4c), normal aggregation occurs. Of greatest importance is the lack of response to collagen suspension, even in concentrations fourfold greater than the minimum effective dose in normal individuals (Chart 4d). From these defective reactions, it is apparent that there is an impairment of platelet ADP release.

Measurements of nucleotide release in these patients (Table 3) after exposure to collagen is decidedly impaired. This impairment is not evident when thrombin is used instead of collagen, as would be expected from the aggregometer tracings. The ability of plasma enzymes to degrade ADP is unaffected in this disorder (Table 3), so that rapid dispersal of the platelets must be explained by some other mechanism. Finally, hemostasis is adequately but temporarily restored with fresh platelet transfusions. This fact is important therapeutically, since patients with von Willebrand's disease respond effectively only to non-contact plasma and not to platelet transfusions, even though both groups may present with identical clinical histories. In addition to the re-

duced Factor VIII levels in von Willebrand's disease, platelet aggregation appeared normal in four cases we comprehensively studied.

Macrothrombopathia<sup>17</sup> is another hemorrhagic disorder in which the bleeding time is prolonged and both platelet adhesiveness and platelet factor 3 availability are impaired. The platelets are large and hypergranular but perform their job poorly. Aggregation by collagen, ADP, and epinephrine is impaired, although clot retraction remains normal. The platelet count may be reduced but the hemorrhagic manifestations and long bleeding time appear out of proportion to the level of thrombocytopenia. Bernard and Soulier<sup>18</sup> first described this hemorrhagic tendency; unfortunately, impairment of platelet aggregation could not be evaluated at that time. We have studied one patient in whom the platelet ATP content was threefold that of a control population. This rise is probably consistent with the size of the platelets, which were often as large as lymphocytes.

Unlike essential thrombasthenia (in which collagen-induced nucleotide release is normal), primary platelet disease and macrothrombopathia have impaired collagen-induced, platelet ADP release. This mechanism is normal in essential thrombasthenia, where the basic disturbance is defective clot retraction and absent platelet aggregation to ADP. There are other bleeding disorders, such as the myeloblastic leukemia case mentioned previously, which fall into this category (Table 1).

In scurvy, the exact nature of the bleeding tendency remains unclear. Ascorbic acid is a cofactor in the hydroxylation of proline<sup>19</sup> (an intermediary step required for the formation of collagen). Its absence therefore readily explains delayed wound healing, but the pronounced mucocutaneous bleeding is less easily explained. Recently, several investigators<sup>20,21</sup> have reported defective adhesion of platelets to glass in scorbutic guinea pigs and also in man. In man administration of vitamin C corrected the defect in platelet-glass adhesion. In addition, Born and Wright<sup>22</sup> have reported that twice the concentration of ADP is required to induce normal platelet aggregation in scorbutic guinea pigs. In our laboratory preliminary controlled investigations of platelet-rich plasma obtained from guinea pigs maintained on a scorbutic diet (supplemented with all other vitamins) for four weeks have shown impairment of ADP aggregation. Partial correction of this defect after incubation with freshly prepared dehydroascorbic acid

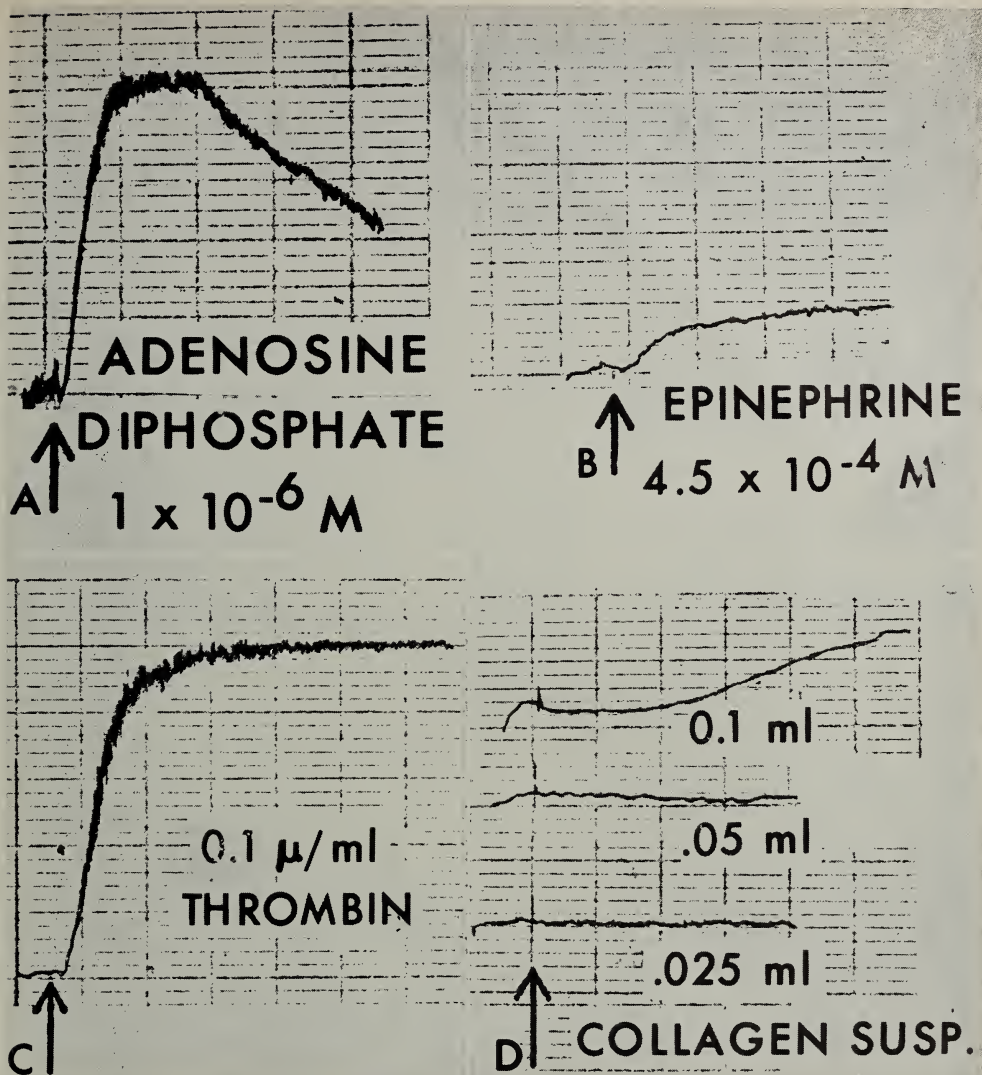


Chart 4.—Platelet aggregation in primary platelet dysfunction as studied in citrated, platelet-rich plasma at  $37^{\circ} \text{C}$  after the addition of collagen, ADP, thrombin, and epinephrine.

(but not ascorbic acid) occurred. This improvement most likely reflects the easier transport of the oxidized form of ascorbic acid across the cell membrane. These findings support the idea that a defect in platelet function in scurvy may exist and may further aggravate the already existing defect in collagen-supporting tissue of capillaries.

The secondary platelet disorders are readily recognized by the existing disease state of the patient,

although occasionally hemorrhage is the first symptom. In uremia impairment of platelet function appears to result from the accumulation of several toxic products, only one of which is urea. Recently guanidinosuccinic acid,<sup>23</sup> a metabolite of an alternate pathway of urea metabolism, has been identified in uremic plasma. It has been shown *in vitro* to inhibit platelet factor 3 activation at concentrations found in uremic plasma. This find-

TABLE 3.—Nucleotide Studies\* of Two Patients with Primary Platelet Dysfunction, Aspirin-Incubated, Platelet-Rich Plasma, and Controls

	Patient		Aspirin	Control
	#1	#2		
Platelet ATP concentration (nanomoles per 10 <sup>9</sup> platelets) . . . . .	35.6	40.4	39.1	37.1
Nucleotide release (nanomoles per 10 <sup>9</sup> platelets)				
Thrombin (0.1 units per ml)				
ATP . . . . .	9.9	11.2	12.5	20.7
ADP . . . . .	5.3	6.0	6.3	11.4
Collagen suspension (0.1 ml)				
ATP . . . . .	1.4	1.1	6.8	13.2
ADP . . . . .	0.6	0.8	2.6	5.4
Plasma ADP enzyme-splitting activity (percent) . . . . .	54.0	50.0	47.2	53.3

\*Nucleotide release was studied in ethylene-diaminetetraacetic acid (EDTA), platelet-rich plasma at 37°C.

TABLE 4.—Effect of Aspirin Administration (0.65 Grams) on Ivy Bleeding Time

Subject	Before Aspirin Administration		2 Hours After Aspirin Administration	
	Bleeding Time (Minutes)	Mean	Bleeding Time (Minutes)	Mean
1	2.5, 3.0, 3.5	3.0	5.0, 6.0, 13.5	8.2
2	1.0, 1.5, 9.0	3.8	4.0, 4.5, 9.0	5.8
3	2.5, 3.5, 5.0	3.7	4.5, 5.5, 5.5	5.2
4	3.5, 4.0, 4.5	4.0	4.5, 5.0, 5.0	4.8
5	1.5, 2.0, 3.0	2.2	4.0, 5.0, 6.5	5.2
6	2.5, 3.0, 3.0	2.8	5.5, 6.5, 6.5	6.2
7	5.0, 5.5, 7.0	5.8	6.0, 7.5, 8.0	7.2
8	2.0, 2.0, 3.0	2.3	3.5, 5.5, 5.5	4.8
9	3.0, 4.5, 5.0	4.2	5.0, 6.0, 6.5	5.8
	Mean	3.5		5.9
	Standard Deviation	1.0		1.3

$$P = <0.001$$

Children's Hospital of San Francisco, 1968.

ing offers some explanation for the frequent disparity between clinical bleeding and the severity of uremia. However, urea cannot be excluded as a contributory factor since Eknayan and coworkers<sup>24</sup> have demonstrated prolongation of bleeding times and impairment of platelet adhesiveness after urea infusions in normal human subjects. In any case, platelet function returns toward normal after dialysis.

In the hyperviscosity disorders, such as multiple myeloma and macroglobulinemia, protein coating of platelets impairs platelet function. In 1959 Pachter<sup>25</sup> demonstrated that reduction of the abnormal protein to monomeric form results in correction of the impaired platelet factor 3 activation. Again, plasmapheresis tends to correct this defect.

Finally, I should like to comment on drug-induced platelet dysfunction. Aspirin and other anti-inflammatory agents, as well as certain vasodilatory compounds, have been shown to interfere with release of ADP from platelets which have be-

come adherent to collagen.<sup>26</sup> Aspirin does not interfere with platelet-collagen adhesion, but it does inhibit the second wave of ADP and epinephrine-induced, platelet aggregation. In addition, aspirin has been shown to have an inhibitory effect on platelet glycolysis. *In vivo* aspirin prolongs the bleeding time, and to some degree the extent of prolongation is closely related to the dosage given. Two hours after ingestion of only 10 grains of aspirin, nine normal subjects had a statistically significant prolongation of the bleeding time (Table 4). Quick<sup>27</sup> has shown that this particular test is important in people with undiagnosed platelet disorders, such as can occur with von Willebrand's disease, especially when the bleeding time appears normal or at least borderline. We have carried out studies of bleeding times before and after aspirin administration on patients with chronic renal disease at the San Francisco General Hospital. In several instances borderline normal bleeding times were prolonged to infinity. In von



Willebrand's disease and primary platelet dysfunction, profound prolongation of a mildly abnormal bleeding time may also occur after aspirin ingestion. I think it is fair to say that when an apparently normal bleeding time is so greatly prolonged by aspirin ingestion, an underlying disorder of hemostasis should be considered. Antiplatelet drugs such as aspirin may have potentially important value as an adjunct in treatment of thromboembolic disease.

DR. SCHMID: Thank you very much, Dr. Sahud. We have a few minutes for discussion. Dr. Aggeler, would you like to comment?

DR. AGGELER:\* I am very pleased with Dr. Sahud's presentation. The greatest satisfaction of a teacher is to be exceeded by his student, and I have had that satisfaction this morning.

The new techniques of investigation are going to be exceedingly valuable in a clinical area. For years we have been plagued with all types of peculiar bleeding tendencies about which we could not do much. I have no doubt that, with these new concepts of platelet function and new techniques for investigation, we shall be able to make some progress.

DR. PERKINS:† Dr. Sahud, the Ivy bleeding times you quoted were remarkably reproducible and consistent within a narrow range. I understand this consistency is the result of a new gadget. Will you tell us about it?

DR. SAHUD: Many times I have looked at the mimeographed data sheets in the Hematology Research Laboratory at Children's Hospital, and I have wondered where the normal range for Ivy bleeding times (one to eight minutes) was obtained. Apparently the range came from an assortment of observations recorded many years ago. Just recently Dr. Aggeler received a copy of an automatic lancet,‡ which has a coil-spring release that enables one to measure accurately the depth of the incision. We have used it to study many patients and have collected data on approximately 50 normal persons. The incision in the skin is remarkably reproducible; nevertheless, we still make three incisions for better accuracy.

DR. BECKER:\* The striking thing in this patient was that he was bleeding intensively even though the platelet count was 150,000 per cu mm. Do you agree that platelet transfusions should be used as treatment in such cases? Can you explain why this particular patient, with a relatively normal white count, was bleeding and what could have been done about it?

DR. SAHUD: I think we could have shaken a little collagen into the platelet-rich plasma to see if any clumping occurred, since this was most likely a problem of platelet-collagen interaction. I do not see any other explanation for this patient's problem. Platelet transfusion is the only possible treatment in this problem of interaction. Why there is an alteration in the platelet membrane, causing failure of normal reaction with collagen, is unclear at this time.

COMMENT: Some of the gastrointestinal bleeding resulted from leukemic infiltration of the stomach wall demonstrated at postmortem examination, but the widespread, massive bleeding was out of proportion to the platelet count.

DR. SCHMID: I must say I am impressed by the development over the last two or three years of more sophisticated recognition of platelet function and dysfunction. I remember vividly that only a few years ago platelets were negligible entities in hematology. Investigators were not sure whether they were dust, stain precipitate, or functioning compounds of the hematological system. Then there was an explosion of syndromes—von Willebrand's disease, Glanzmann's disease, and others—based, at least to those outside hematology, on flimsy clinical or clotting differences. Now suddenly we have new information and find that platelets are by no means mere flakes, but that they are metabolically active, have a very high oxygen metabolism, have a very active shunt pathway of glucose metabolism, and are one of the major factors in initiating the clotting process. It is a most exciting and promising development. I think that in the near future, at least in this phase of clotting, we shall see a good deal of clarification.

\* Charles E. Becker, M.D., Chief Resident in Medicine.

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\*Paul M. Aggeler, M.D., Professor of Medicine (now deceased).

†Herbert A. Perkins, M.D., Associate Clinical Professor of Medicine.

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### Ecology for Survival

LIKE SPRING IN New England, ecology has burst forth almost overnight. Student activists, politicians of all parties and the public alike, all seem to have pounced upon ecology as though it were a blessed relief from the disruptions and negativism which have so recently and so unproductively dominated the scene. Whether this be so or not, a word which even a few months ago was comparatively unfamiliar is now commonplace and the subject matter is receiving national attention.

There is no question that this is long overdue. The interactions between man and his environment are becoming not only matters of health and well-being but even of life or death. For the first time in earth history a living species is in a position to dominate and control its own evolution and to a large extent the environment in which it must live. And for the first time in human history, the land, sea and air frontiers, which seemed so limitless and so obviously there for man's use and exploitation, have begun to close in, leaving man for the first time with no escape, nowhere else to go. All this has changed the rules of the game and changed them profoundly. The reality has only just begun to dawn upon the collective human consciousness. Man lives in a closed biological system which he has the capability to influence profoundly and which itself has the capability to make him ill or to snuff out his very existence.

The nature of this closed system and its implications for human health and well-being, as well as for survival, have so far received only the most superficial examination. As man has prospered and

as his technology and numbers increased, his frontiers and even his resources have been closing in to place unforeseen limits and restrictions upon what he may do or may not do if he would remain healthy, enjoy well-being or even survive as a living species. Within this closed system just about everything affects everything else. If ecology is the term to be used, it should be understood that its subject matter must include not only the effect of man's science and technology upon the environment, but also the vagaries of human nature and human behavior which determine so much of what humans do and do not do. In this sense the social, economic and political systems of man, which reflect human activity, are part and parcel of the overall earth system, the closed biosphere.

The challenge is awesome. Man's domination means that what he does individually and collectively will largely determine the health and well-being of the earth system and its living inhabitants. There is appallingly little knowledge of what should be done, and less still of experience or expertise in how to do it. Beyond the efforts to control population expansion and the pollution of air, land and water which occupy most of the current interest, there are many other even more fundamental problems to be dealt with. Among them are deeply rooted and sometimes less than noble traits in human nature, including some that may be pathological. There are real weaknesses in the ability of any democratic society to make long-range plans of any kind, where the tradition is to oust the incumbents at reasonably frequent intervals, and the game is to plan more for the next election than for the next generation. A further problem is that humanity as a whole is made up of many groups of autonomous peoples who are in various stages of social and industrial development, and whose global concerns are therefore various and often conflicting. Individual humans also are inevitably in various stages of social and



psychological maturity and thus with different and often conflicting values. And perhaps most basic of all will be the question of individual rights. It will be necessary, but difficult, somehow to achieve the necessary discipline in human behavior, whether this be in procreation or whatever, in the common interest of humanity without unduly infringing upon the rights of individual well-being and self-fulfillment for which the human race has been fighting so hard for so long.

For many years there have been pioneering efforts to draw attention to ecological problems and to do something about them. The pioneers are to be found among the family planners and the conservationists. Progress has been slow and opposition from powerful moral and economic interests has been strong. Now quite suddenly ecology is "in." The present danger is that this may prove to be a mere flash in the pan when what is needed is the sustained heat and energy of a controlled nuclear reaction. This is a task not just for the 1970s but for the whole rest of the life span of humanity.

## Carotid Sinus Stimulation For the Treatment Of Angina Pectoris

DURING THE PAST DECADE several important new therapeutic approaches for the treatment of the clinical syndrome of angina pectoris have been developed. It is now generally accepted that the basic cause of angina pectoris is inadequate delivery of oxygen to the myocardium for its demands or needs to perform a specific task. Recently, however, the new approaches to therapy for this clinical condition have resulted from important physiological observations on control of coronary blood flow and a better understanding of hemodynamic and

biochemical factors relating to the initiation of the anginal syndrome. Some of these are a clear demonstration that a rise in arterial blood pressure frequently precedes an attack of spontaneous angina pectoris, that factors which enhance sympathetic nervous stimulation to the heart increase myocardial oxygen consumption by increasing heart rate and the rate at which the left ventricle develops tension,<sup>1</sup> that anaerobic metabolism and lactate production occur during myocardial ischemia, and that the parasympathetic nervous system may play a role in controlling coronary vascular resistance.<sup>2</sup> Utilizing these physiologic concepts, several new modes of therapy have been proposed for treating patients with incapacitating angina pectoris. Propranolol was introduced for treating patients with angina pectoris with the concept that blocking excessive sympathetic stimulation to the heart would allow an individual to perform more work with less demand for increased myocardial oxygen delivery.<sup>3,4</sup> Furthermore, combination therapy with nitrites and propranolol has been advocated to lower blood pressure acutely and to inhibit sympathetic stimulation of the myocardium.

More recently, Braunwald and his colleagues have introduced the concept of carotid sinus stimulation for relieving angina pectoris and allowing patients to perform more exercise without developing angina, or for treatment of established anginal attacks.<sup>5,6</sup> The Specialty Conference appearing elsewhere in this issue presents the physiological basis on which this treatment was introduced and a report of preliminary experience with its use in patients with incapacitating angina pectoris. For many years it has been known that the circulatory response to carotid sinus stimulation included reductions in heart rate, in arterial pressure and in systemic vascular resistance. All of these responses would be expected to reduce angina pectoris, and it was on these principles that Lown and Levine in 1951 proposed a diagnostic test for the relief of angina pectoris by carotid sinus stimulation.<sup>7</sup> A number of physiological studies utilizing the carotid sinus stimulator have clarified the circulatory response to repeated carotid sinus stimulation in awake unanesthetized man.<sup>8</sup> The decrease in arterial pressure, which is far greater than the decrease in heart rate and in cardiac output, appears to be the major factor in preventing the occurrence of angina pectoris and in relieving already established attacks. The observation that patients who use the carotid sinus stimulator for several months

then have less angina and greater exercise tolerance even when not activating their stimulator is interesting and as yet unexplained. Perhaps this reflects the clinical course of coronary artery disease and its unpredictable nature. Braunwald and colleagues clearly recognize the difficulties in assessing treatment for angina pectoris, but they have convincingly demonstrated a significant effect of carotid sinus stimulation in their small, selected group of patients.

The clinical results presented are preliminary, and the authors stress that long-term follow-ups are not available, that the implantation of the stimulation electrodes requires an operation not without risk, that carotid sinus stimulation itself has inherent dangers (death may occur from it), and finally that careful patient selection for the procedure is essential. They also point out that carotid sinus stimulators may be useful in the management of patients with paroxysmal atrial arrhythmias unresponsive to drug therapy.

Although the report in this issue of the journal suggests that the major benefit of carotid sinus stimulation is due to a reduction in arterial pressure, a recent report<sup>2</sup> showed that parasympathetic stimulation to the heart by vagal nerve stimulation (which is equivalent to carotid sinus stimulation in animals) reduced coronary vascular resistance and increased coronary flow. Perhaps this is an additional mechanism by which carotid sinus stimulation improves angina pectoris. These studies must be confirmed and expanded and may lead to other new approaches to the treatment of patients with intractable angina.

From the evidence available, it appears that the technique of carotid sinus stimulation merits further study and more widespread application for the treatment of carefully selected patients with angina pectoris who are resistant to other modes of therapy. Long-term follow-up studies and studies in a group of age-matched and disease-matched control patients will be needed before this unique method of treatment can be placed in perspective.

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## Hemostatic Mechanisms In Thrombogenesis: Implications for Therapy

ELSEWHERE IN THIS JOURNAL Dr. Daniel Deykin has summarized important advances in our understanding of the physiologic mechanisms of hemostasis. He has related these mechanisms to the pathogenesis of the three types of thrombosis seen in patients: the small white thrombus that may occlude a diseased artery; the large red thrombus that may form in a vein or a chamber of the heart; and the fine fibrin thrombi that may be found in the microcirculation after diffuse clotting in the flowing blood. Of practical importance, Dr. Deykin has pointed out how the different role of the blood clotting reactions in these disorders can explain the different effectiveness of anticoagulant therapy in each. Since thrombosis may occur in any patient, physicians in all branches of medicine should profit from a careful reading of his Medical Progress article.

The hemostatic process may be divided into two overlapping steps. In the first, platelets accumulate at the site of vessel wall injury. When the endothelial lining of the vessel is broken, platelets adhere to collagen in exposed connective tissues; interact with the collagen and release ADP; and, as a result of an action of this released ADP, stick to each other to form aggregates. These early aggre-



gates are friable and easily swept away. In the second step, these unstable aggregates are converted into a platelet "cement" by a sealing process in which the individual platelets of the aggregates fuse and are reinforced by a network of fibrin spreading out into the surrounding plasma and extracellular fluid. Thrombin mediates this sealing process. Thrombin also activates an enzyme that stabilizes the supporting fibrin clot by catalyzing a chemical cross-linking of fibrin molecules. Thus, the later reactions of hemostasis depend upon the effective local activation and function of the blood clotting reactions. These reactions are triggered by contact of the blood with collagen; with a cellular lipoprotein, tissue thromboplastin, that becomes available when the vessel wall is injured; and with a phospholipid that becomes available on the altered surface of aggregated platelets.

Traditionally, three mechanisms have been invoked in the pathogenesis of thrombosis—vessel wall injury, an increased systemic coagulability of the blood, and stasis. As Deykin has emphasized, the importance of each varies in the three types of thrombosis. In the small, white arterial thrombus, blood initially continues to flow in the artery and so stasis plays a minor role. The thrombus consists of fused platelets and small amounts of fibrin. Vessel wall damage is paramount, and the thrombus grows because of the same mechanisms that operate to produce local hemostasis after vascular injury. Clotting at the platelet surface results from local activation of blood clotting and not from a systemic increase in blood coagulability. Indeed, it can occur despite a reduced coagulability of the blood induced by the coumarin anticoagulants. Now at last, after two decades of controversy, it is clear that oral anticoagulant therapy rarely prevents arterial thrombotic disease.

The large red thrombus has a very different pathogenesis. It resembles blood that has clotted in a glass tube. It may form in the absence of identifiable injury to the endothelium of a vein. Thus, a red thrombus may be produced in an experimental animal by stopping flow in a normal vein moments after the systemic injection of an activated blood clotting factor. It occurs clinically in circumstances that combine a slow, systemic activation of blood clotting with stasis—for example, postoperatively in an immobile patient with a diminished blood flow in deep leg veins in whom small amounts of activating clotting factors from the surgical site presumably gain access to the

general circulation. Stasis prevents the cellular clearance in the liver of such activated blood clotting factors, permitting them to accumulate and react to form a red thrombus in the stagnant area. Because of the importance of increased systemic coagulability in the pathogenesis of the red thrombus, it is not surprising that coumarin anticoagulant therapy effectively prevents venous thrombosis and pulmonary embolism. Ironically, whereas coumarin anticoagulants have been overutilized in arterial disease, where they have little effect, they have been woefully underutilized as prophylactic therapy for patients with a high risk of venous thrombosis and pulmonary embolism.

Diffuse intravascular clotting results from the release of enough procoagulant material into the blood stream to allow fibrin to form in the circulating blood. Neither local vessel injury nor stasis is involved. The circulating fibrin is deposited as fine thrombi in the microcirculation of many organs. Whether or not these thrombi produce ischemic tissue necrosis depends upon the ability of fibrinolysis, triggered by release of plasminogen activator in the wall of the affected small vessels, to remove the fibrin. Coumarin anticoagulants act neither powerfully nor rapidly enough to stop diffuse intravascular clotting, but heparin will. However, the patient may also have a serious bleeding tendency due to consumption of clotting factors plus the anticoagulant effects of fibrin split products produced by the secondary fibrinolytic reaction. Sometimes the underlying condition causing the episode of diffuse intravascular clotting can be corrected readily, and the decision to use heparin in an individual patient requires a complete assessment of all aspects of the clinical situation.

The recent discovery of drugs that can impede platelet aggregation represents an advance of unknown therapeutic significance. Some of these drugs, such as aspirin and glycerol guaiacolate, are widely used to treat minor symptoms. They deserve particular investigation in arterial thrombotic disease because of the importance of platelet aggregation in its pathogenesis. It is to be hoped that such clinical trials will avoid the mistakes of many earlier antocoagulant trials in arterial disease and will be conducted as controlled, double blind studies.

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## Costly Mythology in Health Care

THE SOCIAL MYTHOLOGY underlying many aspects of health care has received very little attention. There are a number of widely held beliefs which appear to be more or less completely accepted as fact by social, economic and political leaders and by the public. As a result of this acceptance they have become important elements in the health care crisis. Enormous amounts of money are now being spent in the furtherance of these beliefs although, when viewed with detachment, they seem to have many of the characteristics of social or cultural myths. A few more of the more costly of these myths are briefly considered.

*Scientific medicine can bring good health if it is readily available and used correctly.* (Myth)

This belief appears to be widely accepted. It has led to a near equating of good health and good health care delivery. Whenever good results are not achieved someone, be it the delivery system or the practitioner, is held to account. The principle which has emerged and is being applied both to delivery system and to practitioner is *res ipsa loquitur*. The fact of course is that medical science is not exact and never will be, and that the actually quite limited capability of medical practice has been greatly oversold to the public and its social, economic and political leadership. Their resulting efforts to make the dream come true, and to compensate the frustration when it does not, are certainly costly and often wasteful.

*If we simply apply what we know of medical science through better delivery of health care services to all our people, then our morbidity and mortality statistics will be as good or better than those of other nations.* (Myth)

This belief has become widely accepted and, as is usually the case with myths, it has become almost an article of faith in some quarters. Its fallacy lies in an assumption that morbidity and mortality statistics are a reflection of health care services and nothing else. The fact is that no amount of health care services can overcome inadequacies of nutrition, housing, education or economic status—and in this nation the problem is at least as much with these, and with a potpourri of cultural differences, as it is with availability and delivery of adequate health services. A great deal of health care money is being spent in an ill-starred expectation that an improved availability of health care services will bring health to the urban and rural ghettos.

*People will always do what is prudent to protect their health.* (Myth)

Health care professionals and others interested in health care generally are apt to make this assumption. For example, physicians often quite naively assume that patients will always follow their advice. Frequently this is not the case and seldom does the physician discover that his advice is not being followed. Actually it is the nature of man more to risk than to protect his health, whether for excitement or satisfaction or to achieve some purpose. The truth is that the strongest incentives to health care are pain and fear, and even these must be of significant intensity or duration. The myth that everyone will do everything he should do for his health is very real, and substantial waste of money and energy in health care may be ascribed to it. The waste may be found in such things as the dispensing of drugs which are never consumed or the provision of prevention or detection services which often may not be used by those who need them most. It is dangerous indeed to assume everyone else thinks the same way we do, whether we are health professionals or not.

*Practicing physicians have not been able to keep up with progress in medical research and therefore their patients are not receiving the benefits of recent scientific progress.* (Myth)

This belief is of fairly recent origin and appears to result from statements by deans of medical schools and others that the half life of medical

education today is only about ten years, and from an apparent failure of the enormous financial commitment to medical research during the past two decades to bring about a commensurate improvement in health. The facts are that physicians in daily practice probably keep up far better than is generally realized, although this is hard to measure, and that real scientific breakthroughs which bring about dramatic improvements in patient care are far less frequent or numerous than is generally believed. After all much of the research which must be done to bring about these important achievements is basic research with little or no direct bearing on patient care. To satisfy this myth, and without determining to what extent a disparity between medical science and medical practice really exists, costly and time-consuming programs of continuing education are being undertaken in response to public and political pressures.

There are many other cultural myths which lead to waste of the time and talent of health manpower, to higher than necessary costs in health care, and thus to the grand total of the health care crisis. Myths are powerful forces which must be reckoned with in any society. Generally they contain some modicum of truth. They tend to survive in the absence of more precise knowledge. These few we have discussed are no exceptions. They may have even more than a modicum of truth. Scientific medicine *can* be used to improve health. Good health care services applied where they have not been used or available *can* improve morbidity

and mortality statistics. People *do* have an interest in their health, and practicing physicians *do* have difficulty in keeping up. But as yet we do not have the hard data to supplant pervasive myth with incontestable fact. Thus these social myths pertaining to health care not only survive in their all-pervasive force, but give rise to an enormous waste which contributes substantially to the health care crisis.

The cost in dollars of this cultural mythology in health care cannot even be estimated, and without more facts it is unlikely that the cost will be reduced. It is doubtless increased further by another American myth (given credence by the Manhattan Project and the Apollo program)—that if one is willing to spend enough money anything can be accomplished. There is evidence that this principle too has been applied in health, first in research in health sciences, and more recently in the financing of health care. Apparently forgotten, unfortunately, was that both know-how and resources must be available for this approach to be successful.

But in any case, and for better or worse, social and cultural myths are not to be discounted in American society, nor is their effect upon the cost of health care and on the health care crisis. Paul Ward, Executive Director, California Committee on Regional Medical Programs, has put it well: "In an organized society such as ours, and especially in the field of social programs, dominant myths are often more real than reality itself."

# The Concept of Mainstream Medicine For All Californians

## Fifth Progress Report of Committee On Role of Medicine in Society

### PART II

*This Fifth Progress Report is being printed in three parts in CALIFORNIA MEDICINE. Following the appearance of Part III the report will be bound in a pamphlet which may be ordered at \$1 a copy from 693 Sutter Publications, Inc., 693 Sutter Street, San Francisco, California 94102.*

THE FIRST SECTION of this *Fifth Progress Report* of the Committee on the Role of Medicine in Society sought to establish that "mainstream medicine" is the best, if not the only instrument which can practically be developed to render "comprehensive health care" for all Californians and surveyed in broad fashion the scope of the problems to be solved. The Committee believes that a number of basic actions which have already been taken in fact commit the California Medical Association to work actively to achieve the goal of "Mainstream Medicine for All Californians." What is now needed is an acceleration of the process of decision and action within the Association to match the pace of social change. The Committee therefore, in Part II of this report, identifies six subject areas which it believes are in urgent need of greatly improved technology, and then, in Part

III, proposes a comprehensive action program for organized medicine in California. These are as follows:

- Health Teams
- Centralization and Decentralization of Services
- Health Care Plans and Financing Health Care
- Cost Benefit Assessment
- Technology for Leadership
- Guidelines and Their Uses

Each of these has to some extent already been recognized by the California Medical Association as a matter of proper concern to the Association and in each there is some record of experiment, innovation and experience. The Committee believes that what is now needed is a greater sense of urgency, something in the nature of a "crash program" to develop the needed technology and to master whatever is necessary to apply it effectively, with a much keener appreciation of elapsing adaptation time in relation to the rate of environmental change.

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Committee on Role of Medicine in Society: Burt L. Davis, John B. Dillon, Sanford Feldman, Elmer F. Goel, John T. Saidy, Marvin J. Shapiro, Malcolm C. Todd and Malcolm S. M. Watts, chairman; and, ex-officio, Henry V. Eastman and E. Kash Rose.

Part I of this report appeared in the February, 1970, issue of CALIFORNIA MEDICINE.



## Health Teams

The "permanent" overall shortage of physicians alluded to in Part I, and particularly of specialists in general or family practice (the theoretically ideal primary physician), and the inevitably uneven geographic distribution of doctors, not to mention increasing physician specialization other than in general or family practice, all make necessary the greater use of health teams in every aspect of health care. There is actually ample precedent. Physicians have worked with other physicians, nurses, technicians and other health professionals for centuries. More recently they have also begun to use inanimate automated techniques in their practices. What is new is the greater need to use both these human and inanimate aids to extend substantially the reach of the practicing physician and at the same time improve the individual personal relationship at the point of contact with the patient or consumer. This is of particular importance with respect to those large groups of patients whose backgrounds and life styles may be quite unfamiliar to the average physician and whose awareness of their own needs remains to be developed.

If a health team may be defined as "a number of persons in the allied health professions and other health personnel associated together to accomplish a common objective in health care by cooperation and coordinated action"\* then there is good reason to expect that much mainstream medicine will be practiced within the framework of health teams of various kinds, and that these will evolve from the beginnings which have already been made.

The Committee believes that for these reasons the nature of health teams urgently needs study by mainstream medicine. Team dynamics, communications, responsibilities, education and satisfactions need to be better understood. It is more than likely that practicing physicians will need to be educated in new skills with respect to team uses and team operations, and it is certain that the roles and training of team members must be more closely related to one another. In a similar vein consumers will need to learn more of the availability of health care and the desirability of entering the health care system.

The Committee commends the report on the "Education of the Physician as a Team Coordinator" from the Second Planning and Goals Conference, endorses the Council action referring it for implementation, and urges that this subject be studied promptly and in depth.

## Centralization and Decentralization Of Services

The need for health teams merges into the need for study and further refinement of the organization of health care delivery. The mainstream requirement of "help near one's home" and of "equal access to a single level of high quality health services" must somehow be reconciled with the facts that it is unlikely that a sufficient number of physicians can ever be attracted to isolated or deprived communities, and that even if this would be done the necessary consultation, facilities and equipment could still be lacking. Provision must also be made to accommodate the larger intake into mainstream medicine which will inevitably result from screening procedures, outreach programs, population growth and longer survival, recognizing that there cannot be an expansion of resources sufficient to meet these needs in the traditional way.

For reasons such as these it appears both necessary and urgent to develop appropriate criteria for both centralization and decentralization of health care services. There is need to determine what are the critical masses for centers of various kinds, the critical services to be rendered in the non-centers, and the critical linkages between the centers and the non-centers. As these criteria are developed with attention to all the scientific, human and economic values which are involved, the appropriate use of health teams and mechanical aids and the need of every patient to have a significant relationship with at least one physician, they will provide the incentives for mainstream medicine to evolve the organization which will be needed to give mainstream care to all Californians on a voluntary and cooperative basis.

The Committee believes that the subject of centralization and decentralization of health care services in urban, regional and rural areas urgently needs study, and that this study should be done within mainstream medicine if the results are to be well received by both the health care professions and the public.

\*Second Planning and Goals Conference, CMA Committee on Continuing Education, February 22 and 23, 1969, San Diego, California

## Health Care Plans and Financing Health Care

Previously in this report it was noted that universal coverage for all persons for health care, through either the private or public sector or some combination thereof, is an inescapable corollary to the right of access of all to high quality health care. If this is true, and realistically it is, then some acceptable means must be devised to render high quality health care within some kind of framework of universal coverage.

Mainstream medicine, particularly in California, has an enviable record of experiment, innovation and experience in improving health care plans and the financing of health care services. One need only mention pioneering programs such as California Blue Shield (formerly known as California Physicians Service), the relative value studies, the foundation plans, and the Medi-Cal Program as examples. Group practice, both prepaid and fee for service, has been successfully developed in a variety of forms, and it is worth noting that one small closed panel, prepaid plan has been in continuous operation in San Francisco for over 100 years. In the interest of being complete, there is also a long-standing compulsory governmental health care plan in which the employees of the City and County of San Francisco must participate by law, and at the state level the Public Employees Retirement System has developed the role of government as an employer in relation to improving health care plans and their financing. Thus mainstream medicine in California has a broad base of experience and a pluralism of approaches upon which to build.

The next steps may be difficult but are not impossible. Pluralism and free enterprise should be preserved and strengthened. First, health care plans must be developed which provide for comprehensive services including prevention and rehabilitation. The California Medical Association has made a beginning by adopting some "Guidelines to Components of an Adequate Program of Health Care Coverage" on 11 January 1969, approving some recent recommendations of the Ad Hoc Committee on Health Care urging further experimentation, and in pressing for a national program for accreditation of health care plans. Secondly it is essential that these plans have portability. This term has several usages. It may refer to a freedom to change from one type of health care

plan to another more or less at will, it may mean the ability to carry one's protection from one job to another or from one occupation to another, or it may pertain to the geographic portability of coverage. Certainly, in today's mobile society, it will not for long be enough to have the coverage only local as is so often the case with closed panel prepaid plans. Means must be found to make the coverage effective wherever one is in the state, the nation, or even the world. Again there is a growing experience in the private sector upon which to draw. And thirdly, an answer must be found to the need for compulsory financing. Here some combination of private and public financing would seem to be the most realistic approach and here there are precedents to be studied.

The Committee suggests that two assumptions might be made. First, it is desirable that there be a pluralism of health care plans and that these be developed within the private sector, and second, that government is responsible to finance or assist in financing the medical care of those individuals who are "eligible" by appropriate criteria. With these assumptions in mind it is then suggested that health care plans be designed to prepay the health care expenses so as to meet the needs of the majority of those who will require services, that guidelines be developed for such plans and that the principle of voluntary accreditation be applied to give them recognition and approval. It is then also suggested that "eligibility" for government financing of an individual's health care might occur by virtue of (a) an individual having exhausted the benefits of "accredited" health care plan for his illness (one designed to meet the needs of the majority), or (b) being in an income or disability bracket which would merit a government contribution to the premium of such an accredited health care plan. Central to this proposal is a recognition that any person will have fulfilled his responsibility for financing his health care by participating in an accredited health care plan. These suggestions assume government recognition of voluntary accreditations of health care plans and there is considerable precedent for government recognition of voluntary accreditation.

The Committee believes that participation in such an accredited basic plan could properly be made compulsory. Again, there is substantial precedent for this with automobile insurance, unemployment insurance, etc. It also believes that such an arrangement could preserve the domi-



nant role of the private sector in health care delivery including a major role in the financing of basic health care, and yet permit government financing where there is the greatest stress on private financing, i. e., when a patient has inadequate resources or when he has exhausted his reasonable and approved health care benefits. In this proposal the incentives for and the means to accomplish quality, efficiency and utilization control would remain primarily with the private sector.

The Committee believes that the pluralistic base and the tradition of experiment and innovation which characterizes mainstream medicine in California must now be turned to account to make health care plans more comprehensive and the financing a more realistic cooperative venture of the public and private sectors. This is a task in urgent need of study and prompt action.

### Cost Benefit Assessment

There is pressing need to develop more experience and new technology in cost benefit assessment. Health care is the fastest growing industry in the wealthiest and most technologically advanced nation in the world. Costs are rising and appear to be rising faster than the benefits. Indeed, if the present rate of cost increase continues, it has been estimated that by 1984 the health care industry will consume 100 percent of the gross national product. Benefits are inequally distributed and there is some suspicion that new progress in medical science is not being promptly or sufficiently reflected in health care delivery. Walter Reuther has complained that "53 billion dollars are now being spent annually for health care yet the existing financial structure does not provide us with any leverage by which to discipline either the cost, the quality or the coverage."\* Clearly this has become a serious problem which is of the greatest concern to mainstream medicine. The pressures to deal somehow with the "national crisis" in health care are building up very rapidly and there is some danger that an emotionally determined solution may be in the offing unless fact and reason can be brought to bear quickly.

The Committee suggests that the technology of cost benefit assessment in health care does not yet exist although various attempts are being made to grapple with the problem. Four areas of study are presented for urgent consideration:

- *Those increases in health care costs which reflect the economic impact of scientific progress and social change should be clearly identified and separated out.* These would include the effect on health care costs of new and improved science and technology; of the increased longevity and overall population growth which result from application of this technology; of the greater use of services by more people as the principle of equal access gains ground; and of general economic factors such as rising costs of labor and supplies in particular, and the effects of monetary inflation in general.

- *There is need for more study of health care benefits in terms of their effectiveness and cost.* More accurate data are needed concerning certain preventive measures, such as routine physical examination, multiphasic screening, routine Papanicolaou smear tests, and the like; diagnostic tests of various kinds; therapeutic agents and procedures; and many rehabilitative programs with respect to their proper indications, utilization characteristics, costs and value in patient care.

- *The present efforts to achieve objective cost analysis in health care should be continued and intensified.* The upward spiral of health care costs has produced a clamor for more efficiency and even price controls. Much of the focus has been on the medical profession and professional fees. Experience shows that the medical profession and professional fees contribute a comparatively small part to costs. Also many attempts at arbitrary control of either fees or services, whether by the private or public sector, have always resulted in greater inefficiencies and ultimately greater costs. There is urgent need for realistic analysis of costs and efficiency in every aspect of health care delivery.

- *A technology for quality assessment in health care is acutely needed.* Quality and cost are linked in health care, as indeed they are in almost everything else. Value received for dollars spent cannot be determined without some assessment of the quality of what is purchased. The Committee has previously recommended (1967) that the CMA "assume the responsibility for attempting to develop an Index for the Assessment of the Quality of Medical Care and, if such proves possible, to assume the responsibility for its appropriate application." The need to do this remains as imperative as ever.

### Technology for Leadership

There is a growing consensus within organized medicine, and it is the opinion of the Committee, that the medical profession should play a leadership role in the evolution of mainstream medicine. Effective leadership depends upon motivation which is acceptable, aims which are consistent with these motives and a satisfactory performance which is evident to the membership and the public. There must be a strong base of supportive professional and public opinion. There must be a well developed technology for effective action and there must be public accountability for stewardship. So far medical organizations have made relatively little conscious effort to cultivate and strengthen a number of these essentials of organizational leadership.

\*Walter Reuther, *Am. J. Pub. Health*, 59:18, 1969



## Motivation and Competence

Elsewhere the Committee has reported on an ideological basis for medicine's position, i. e., its competence in human biology, its concern with human individuality, and its commitment to progress. This ideology underlies the motivation, purposes and performance of organized medicine in the interests of advancing medicine and betterment of the public health. A role of leadership requires that an organization be respected for its motivation, purpose and performance. Its objectives must be regarded as unselfish, in the public interest and must become equated with the best interest of the members. The competence of the organization in general and also with respect to whatever the specific issue, must be clearly established. Facts must be determined, objectives analyzed, sound and feasible recommendations developed, and valid supporting arguments prepared for use in the action phases of organizational leadership. Above all, performance must be consistent with motivation and policy statements.

## Support

Leadership requires strong support to be effective. In mainstream medicine effective organizational leadership requires the support of public opinion and of membership opinion. In democratic societies, whether political or professional, the majority opinion is the ultimate force which in the long run determines the ideological, social, economic and political course to be followed. The Committee believes that the importance of informed public and professional opinion needs more recognition and attention than it has so far received and that the technology of developing supportive attitudes should be promptly studied and developed by organized medicine. Such support is absolutely essential for effective organizational leadership.

## Action Tactics

The Committee believes there is need for organized medicine to develop and refine its skills in the technology of action tactics if it is to be an effective leader in mainstream medicine. Action is usually more effective than reaction. The bases of action tactics are obviously "what to do" and "how to do it." The "what to do" must be based upon a factual knowledge of the subject matter measured against scientific, humanitarian and economic values\* which are often in conflict with one another. The decision reached should be sound, preferably innovative, realistic, and clearly expressible in terms of the patient and public interest. The "how to do it" tactics entail appropriate uses of pressures, negotiations and

the law. Pressures can be social, economic and political, as can negotiation, depending upon the subject matter. Action tactics with respect to the law may involve efforts to change the law or a resort to the courts.

*Social pressures* are exerted primarily through communication, involvement and persuasion. Persuasion can be effective if what is sought is reasonable, if the supporting arguments are valid, if it is consistent with patient and public interest and if there is public sympathy with the organization and its purposes. The technology of persuasion needs further development and better organization.

*Economic pressures* are now being exerted in mainstream health care by providers (c. f., nurses, associations), by labor unions both as health workers and as consumers, and by government through certain arbitrary and discriminatory reductions in normal fees for service rendered. When set upon, whether by friend or foe, there are only four possible responses—run away, surrender, retaliate, do nothing (i. e., neither surrender, retaliate or run away). Running away, surrendering, or "doing nothing" all leave the advantage entirely to the assailant. However, if a counterforce is applied there can result victory, defeat or a balance of power. Physicians render an essential service to society. Economic power tactics are now accepted practice in the health care field, and the Committee believes that organized medicine should promptly develop a realistic technology for economic counterforce and be prepared to apply it as and when necessary.

*Political pressure* may be direct, upon an elected official whose campaign was or might be supported (with due regard to the possibility that the opposition may have supported him as well, or better), it may be indirect through the actions of other organizations or agencies of like purpose, or through a well-informed public opinion. The Fourth Progress Report (April 1968) called for a better technology for organizing advocacy and the Committee believes that the need for such a technology is great if political action is to be as effective as it should be in today's society.

Negotiation may be desirable and indeed necessary when something like a balance of power is achieved as a result of exercising social, economic and political pressures. Negotiation is best carried on by skilled persons from a position of social, economic and political strength. The terms sought must be reasonable, the supporting arguments valid, and the whole consistent with the interests of the profession, the beneficiaries and the public. Negotiations are most productive when they are to the mutual advantage of both parties. The Committee believes that medical organizations must develop the technology and machinery for negotiation as an essential for leadership in mainstream medicine.

*Legislation and legal action* are nothing new to the California Medical Association and, indeed, the Committee believes that in this area the CMA has not only pioneered the technology but has perfected it to the point where its leadership is unquestioned. For the benefit of others who may be less experienced, it is suggested that legislative or court action be in the public interest and interpretable as such, have public support or, if controversial, the support of a majority of politically influential groups, and be reasonably consistent with announced policies of the association. Legislation proposals should be such that they are politically possible for legislators to accept and support.

*Public opinion* is a powerful support mechanism for social, economic and political pressures, for negotiation, and for legislative and court action. It is emphasized once again that the technology of action tactics depends in the ultimate analysis upon an informed and favorable public opinion for its success. Once again the Committee urges that a better technology for understanding and informing public opinion be developed.

\*The Fourth Progress Report of the Committee (April 1968) examined scientific, humanitarian and economic value systems in health care, noted that they are inevitably in conflict, and proposed a concept of "flexible advocacy" as a means for organized medicine to maintain an appropriate balance among them. Scientific values pertain to quality, humanitarian to equality, and economic to costs. Medicine is concerned with the first by virtue of its competence in human biology, the second because of its interest in human individuals, and the third because of its commitment to progress.

## Public Accountability

Public accountability is a new concept for medical organizations. It is an important device to improve public understanding, emphasize the competence of the organization, gain recognition for its accomplishments to date and support for its advocacy of what still needs to be done. A periodic accounting of his stewardship provides an important stimulus for a leader and promotes confidence among the led. The Committee believes that periodic authoritative reports of progress and problems in health care are essential for leadership in mainstream medicine.

## Guidelines and Accreditation

Mainstream medicine has a very considerable experience with the use of guidelines as a device to indicate what is acceptable and necessary, and with the use of voluntary certification or accreditation to recognize that the guidelines have been followed. This technique provides a flexible framework within which essentials can be met but which at the same time encourages experiment, innovation and improvement. It connotes something far more than set standards or precise specifications. The California Medical Association has developed guidelines for many purposes and has applied the principles of accreditation in a number of circumstances.

The Committee believes that this proven mechanism can now become the means by which the paradox of a single level of high quality health care for all Californians, yet with local options and local control, can be solved.

It would be entirely possible to develop guide-

lines not only for such things as physician hospital relationships, but for health teams, for the centralization and decentralization of health services, for health care plans and for the financing of health care and for cost benefit assessment. They can even be created for many of the techniques and much of the technology of leadership by medical organizations. If all these guidelines were to come into being and become widely implemented as a result of the incentive of certification or accreditation they would in fact constitute a valid framework or structure within which mainstream medicine for all Californians could become a reality and with the great advantage that the framework would be constantly subject to peer review and peer improvement while the research development and control would remain primarily in the flexible and innovative private sector of our society.

*The Committee recommends that the Council undertake a "crash" program of study and research to develop an improved technology for health teams, centralization and decentralization of health services, health care plans and financing of health care, cost benefit assessment, leadership techniques and appropriate guidelines in each of these and other appropriate areas, which when taken together might constitute a kind of flexible framework for "mainstream medicine for all Californians."*

(Part III will be published in the next issue.)



## "California Invitational"

# Malpractice Prevention Workshops

## A Progress Report

THE ESCALATING AND potentially catastrophic professional liability crisis prompted the California Medical Association, California Hospital Association, California Nurses Association, Hospital Councils of Northern and Southern California, and the carriers, to sponsor a unique series of 17 malpractice prevention workshops throughout California. Under the general title "California Invitational" these workshops sought to find ways to alleviate the malpractice problem by confronting the pertinent and practical problems related to the everyday provision of health care.

Unlike other patient-care oriented meetings, the "California Invitational" regional workshops placed the burden upon the participating physicians, hospital administrators, nurses, defense attorneys, insurance executives, and others interested in the health care field, for their ideas on how best to upgrade patient care. From the beginning, it was the consensus that any improvements in patient care were first contingent upon improvements in communications. Those who attended the workshops repeatedly and consistently emphasized the need for:

- Better professional-patient communications
- Better inter-professional communications
- Better continuing education communications

Each "California Invitational" regional workshop was divided into eight specific discussion sections:

- I. Elopement and Suicide
- II. Anesthesia
- III. Surgical Cardiac Arrest
- IV. Emergency and Floor Cardiac Arrest
- V. Requirements for Assistants in Surgery and Surgical Privileges
- VI. Infection Control
- VII. Maternal and Neonatal Injuries
- VIII. Injection Injuries

The following progress report synthesizes and summarizes many of the comments and suggestions presented at the first series of these regional malpractice prevention workshops.

The delivery of health care is an on-going, developmental art and science. Similarly, this progress report is a continuing project, and it is anticipated that these progress notes do not contain all of the answers. Suggestions and ideas are solicited. Any reader who has a contribution to make beyond the ground covered in the following progress notes should communicate it to his own professional organization for presentation at future workshops.

To advance patient care and to minimize errors or omissions are the goals of "California Invitational." Establishment of standards is not a goal; although, in the course of time and by general acceptance, some of the concepts emanating from these grass roots conferences may achieve this status. In the meantime, it is hoped that the present report will be thought-provoking, and will stimulate all individuals in the health care professions to work toward the stated goals of the California Invitational malpractice prevention workshops.

### SECTION I—ELOPEMENT AND SUICIDE

#### *A. Medical Evaluation of the Psychiatric and Medical/Surgical Patient's Propensity Toward Suicide and/or Elopement*

1. Each hospital and its medical staff should convene a committee of the medical staff, to identify signs and symptoms characteristic of suicide and elopement potential among patients in said hospital.

2. The medical staff and nursing, jointly, should train and educate members of the medical staff, nursing and other responsible hospital per-

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sonnel in the recognition of such signs and symptoms and their respective duties for suicide and elopement avoidance.

3. When suicide, elopement or an attempt at either occurs in the hospital, the committee should analyze the individual's history with special emphasis upon the few weeks or months immediately prior to the occurrence, to identify contributing factors, if possible.

4. Such committee might include outside psychiatric consultants when necessary.

5. In psychiatric hospitals and in general hospitals with psychiatric departments, this committee's function could be the responsibility of the psychiatric supervisory committee.

6. The admitting physician should record in his patient's medical record any information indicative of potential suicide or elopement.

7. Patient's charts should include comments relating to the patient's behavior while in the hospital, including pertinent statements made by the patient.

#### *B. Timely Communications*

1. The nursing staff should communicate their own observations concerning potential suicide patients, to attending physicians and to designated hospital staff personnel.

2. The fact of communication, and the signs and symptoms which lead the nurse to make that communication, should be documented in the medical record of the patient.

3. All hospital personnel should be instructed to report unusual patient behavior to the nursing staff.

4. In response to such information, the nursing staff should investigate and, if indicated, communicate and record such information in the manner previously described.

5. The attending physician, or in the event of his inability to respond promptly, the hospital administration or its delegate, should take action appropriate under the circumstances.

6. Such action may include, but need not be limited to, the following:

- Request for a psychiatric consultation
- Augment patient supervision, and
- Transfer of the patient to an appropriate psychiatric facility.

7. Attending psychiatrists should formulate and write orders, upon admission and subsequent

thereto, which are clear, adequately detailed, and in conformance with the capabilities of the hospital.

#### *C. Leaves of Absence*

1. When an authorized leave of absence is contemplated the attending physician should confer with the family and/or the prospective custodian to determine the feasibility of such a leave.

2. All reasons for authorized leave of absence should be recorded by the attending physician, and by the consulting psychiatrist, if any, in the patient's chart.

3. When a patient with noticed elopement and/or suicidal tendencies is removed from the hospital without the authorization of the attending physician, such removal should be documented on the chart.

#### *D. Open vs. Closed Ward Therapeutic Management*

1. The medical staff in any psychiatric hospital, or the psychiatric department in any general hospital with acute psychiatric facilities, should review and analyze the physical and service facilities and capabilities of the particular psychiatric hospital or unit.

2. Such a review might include a determination of which patients, with particular reference to patient conditions involving suicidal and elopement potentialities, may not safely be admitted to the particular hospital or unit.

3. Physical restraint and/or use of a seclusion area or closed ward setting might immediately be utilized, as a temporary measure, until such time as the attending physician can personally respond, if:

- The patient is actively suicidal, and/or hyperactive to the point that the patient has to be physically restrained.
- The patient is assaultive towards others, destructive towards property, and/or a real threat to himself.
- The patient is grossly confused as in the case of over-usage of drugs, delirium tremens, or alcoholism, and is consequently unmanageable without restraint.

4. Temporary admittance to the psychiatric ward of a general hospital, or to a psychiatric hospital from a general hospital, of a consenting in-hospital patient might only require the written

order of the attending physician and one consulting psychiatrist, subject to the review of the attending physician and the consulting psychiatrist at each 24-hour interval.

## SECTION II — ANESTHESIA

### *A. The Professional Anesthetist*

#### **Pre-anesthesia**

1. It is suggested that the preoperative visit should, except in occasional and unavoidable circumstances, be conducted personally by the anesthesiologist scheduled to care for the patient at the time of surgery.

2. At the time of the preoperative visit, there should be a disclosure of the plan for anesthesia and an acceptance thereof by the patient or by a proper representative.

A preoperative note of the findings relating to anesthesia, of the plan of anesthesia and the acceptance thereof, should be set forth in the patient's medical record.

When reasonably possible, any conflict between the operating surgeon and the anesthesiologist with respect to the type of anesthesia to be administered should be resolved prior to the time a plan of anesthesia is disclosed.

3. When a serious question is raised regarding the readiness of the patient for anesthesia for elective surgery, such surgical procedure should be postponed until such time as there has been an adequate reevaluation.

4. A complete history and physical should be available on the patient's chart at the time of the anesthesiologist's visit to the patient. However, such documentation should not replace the anesthesiologist's own responsibility for personally evaluating the patient.

5. The surgeon and/or the attending physician should share a responsibility to communicate to the anesthesiologist and to so record on the chart, unusual problems known to them which may affect the administration of anesthesia.

#### **Anesthesia**

1. The person administering anesthesia should be in constant attendance and constantly monitoring the patient while under anesthesia.

2. The methods of monitoring employed should be recorded on the chart.

3. The use of the esophageal stethoscope or

precordial stethoscope should be considered when deciding the plan of constant monitoring.

4. Safety warning mechanisms of proven efficacy should be utilized whenever and wherever feasible.

5. If no anesthesiologist is physically present in the operating room, the surgeon should assume responsibility for medical supervision of the administration of anesthesia.

6. During anesthesia, vital signs, including systolic and diastolic blood pressure, heart rate and respiration should be monitored and contemporaneously charted.

7. During anesthesia, in the absence of an anesthesiologist or anesthetist, vital signs should be monitored and recorded by a person designated by the surgeon.

8. On admission to surgery blood pressure, drugs and dosages, including indications therefore and time of administration thereof in surgery, should be recorded.

9. An accurate description of any unusual incident in the operating room and steps taken to remedy same, should be fully charted at the earliest possible moment after the termination of any emergency.

10. Local anesthetic agents used, concentration and quantity, should be noted on the chart.

#### **Post-anesthesia**

1. Patients should not be removed from surgery until the person administering anesthesia is satisfied with the patient's stability and has so recorded on the chart.

2. The care of the post-anesthetic patient should not be delegated by the anesthesiologist or surgeon to the post-anesthetic care facility nurse until the anesthesiologist or surgeon has ascertained that the patient's condition is such that the patient may safely be transferred from the immediate supervision of a physician to that of a post-anesthetic care facility.

3. The status of the patient at the time supervision is transferred to the post-anesthetic care facility should be recorded on the chart by the physician responsible for the anesthesia.

4. The physician responsible for the anesthesia should discuss the care of the patient in the recovery room, including possible oxygen therapy, with the recovery room nurse at the time the general care of the patient is passed to the nurse.

5. Subsequent visits by the anesthesiologist or



surgeon to the recovery room should be recorded in the nurse's recovery room record.

6. If no anesthesiologist is involved in the care of the patient, the surgeon should perform those duties in the recovery room for which an anesthesiologist would normally have been responsible.

7. The medical staff should establish criteria for the discharge by nurses of patients from a post-anesthetic care facility.

8. Patients should not be discharged from a post-anesthetic care facility to an intensive care unit or to the nursing floor until the physician responsible for anesthesia has noted, in writing on the patient's chart, that the patient may be discharged, or until the nurse in charge has noted that the criteria for discharge have been met.

#### *B. Other Issues as Developed*

1. Anesthesiologists in each hospital should adopt an anesthesia record which shall minimally include that information now contained on the standard anesthesia record approved by the American Society of Anesthesiologists.

2. At least one member of the medical staff in surgery and selected operating room personnel, as well as the individual administering anesthesia should be proficient in the performance of cardiac resuscitation.

3. Those persons administering anesthesia should be proficient in the performance of endotracheal intubation.

4. Staff privileges of those persons administering anesthesia should be reviewed on an annual basis.

5. When feasible, a Department of Anesthesia should be organized in each hospital.

6. Operating rooms should be equipped with an electric clock with sweep second hand.

### SECTION III — SURGICAL CARDIAC ARREST

#### *A. Pre-arrest Preparation*

1. Except under emergency conditions, a complete history and physical should be available on the patient's chart at the time of the anesthesiologist's preoperative visit to the patient. However, such documentation should not replace the anesthesiologist's own responsibility for personally evaluating the patient.

2. When he is not the attending physician, the surgeon should personally evaluate the patient and

enter in the chart his findings and recommendations.

3. The attending surgeon should perform, for each surgical patient, a preoperative evaluation within the 24-hour period immediately preceding surgery; this is in addition to any previous physical examinations.

4. The surgeon and/or the attending physician should record on the chart and communicate to the anesthesiologist unusual problems known to them which may affect the administration of anesthesia.

5. Essential laboratory work, as defined by the appropriate medical staff committee, should be on the chart before elective surgery.

6. Except in an emergency requiring immediate action, if the anesthesiologist believes that the patient's condition may create an abnormal anesthetic risk, his opinion should be communicated to the surgeon and the fact of such a communication should be noted in the medical record and acknowledged, in writing, by the surgeon.

7. Except in occasional and unavoidable circumstances, the preoperative visit should be conducted personally by the anesthesiologist scheduled to care for the patient during surgery, and should be recorded in the patient's medical record.

8. Immediately prior to surgery, the surgeon should note and record the patient's current condition, relative to the proposed operation.

9. The surgeon and his assistant, when one is required, should be present in the surgical suite before anesthesia is induced.

10. Except in occasional and unavoidable circumstances, preoperative orders for medication should be formulated by the anesthesiologist who is to give the anesthetic during surgery.

11. Electronic monitoring devices should be used only as secondary means of monitoring.

12. All hospitals and clinics where surgery is performed should have equipment and supplies, and instructions for the use thereof, for the treatment of cardiac arrest as outlined by the American Heart Association Committee on Cardiopulmonary Resuscitation. (See AHA pamphlet "Emergency Resuscitation Team Manual: A Hospital Plan.")

13. Adopted resuscitative measures should be printed and posted in all operating rooms.

14. Persons administering anesthesia should be competent in a variety of methods of anesthetic administration; and, in the techniques and instru-



mentation required or potentially necessary for safe care of the patient.

15. The person administering anesthesia should constantly attend and monitor the patient under anesthesia. Should the person administering anesthesia be replaced, this transfer of responsibility should be noted on the chart.

16. Vital signs, including systolic and diastolic blood pressure, heart rate and respiration should be monitored and contemporaneously charted during anesthesia.

17. In the absence of an anesthesiologist or anesthetist, such vital signs should be monitored and recorded by a person designated by the surgeon.

18. At least one member of the medical staff in surgery and selected operating room personnel as well as the individual administering anesthesia should be proficient in the performance of cardiac resuscitation.

19. Members of the medical staff performing surgery should demonstrate proficiency in cardiac resuscitation, at least annually.

20. Selected operating room personnel should demonstrate proficiency in cardiac resuscitation, at least annually.

#### *B. Post-arrest Action*

1. Each medical staff and hospital administration should jointly develop an "Emergency Arrest Record Information Sheet"; and, one person may be designated, at each surgery, to record the events should an arrest occur.

2. Steps should be taken to assure that at regularly scheduled intervals, all resuscitation equipment in the hospital is inspected and calibrated (if necessary) and that such inspection is documented.

#### *C. Other Issues as Developed*

1. Hospitals should provide an adequate system to expedite transcription of dictated physicals and histories.

### **SECTION IV — EMERGENCY AND FLOOR CARDIAC ARREST**

#### *A. Non-surgical Cardiac Emergencies*

1. Each hospital, regardless of size, should promulgate and maintain an effective program for emergency cardiopulmonary resuscitation.

2. Each medical staff should share responsibility with the hospital for development and implementation of a program for emergency cardiopulmonary resuscitation.

3. Such a program should designate the responsibility for action of particular classes of personnel according to time, place, and function, and according to the characteristics of the particular hospital.

4. All members of the medical staff and selected hospital personnel should be familiar with the techniques of cardiopulmonary resuscitation.

5. Each medical staff should implement an educational program, which could include training in cardiac massage, respiratory assistance and defibrillation for physicians and selected hospital personnel.

6. Medical staffs may consider the demonstration of competency in the performance of cardiac massage, respiratory assistance and defibrillation as one prerequisite for medical staff appointment or reappointment.

7. Cardiac resuscitation carts should be checked at the beginning of each nursing shift by designated personnel.

#### *B. Heroic Resuscitation Measures*

1. Each medical staff should adopt its own policy, preferably in writing, regarding heroic resuscitation; however, the decision concerning any individual patient remains at the discretion of the attending physician.

#### *C. The Coronary Care Unit*

1. When feasible hospitals should have available a special arrangement or facility for the care of patients with acute heart disease.

2. The type of arrangement or facility developed should be the result of planning by the hospital and its medical staff and should be adapted to the requirements and resources of the community.

3. Except as set forth in the following paragraph, the decision whether or not to admit a particular patient to such a facility should be left with the attending physician; provided however, the propriety of the attending physician's decision may be the subject of medical staff committee review.

4. The medical staff should develop criteria for bed priorities in the facility as part of the facility care plan and should appoint a responsible staff member for administration of such a priority system.

5. Medical supervision may either be retained by the attending physician or be assigned to a departmental medical director as determined by medical staff policy; provided however, the departmental director should be authorized to provide or render emergency services as required.

6. Cardiopulmonary resuscitation, when performed by registered nurses, should be subject to the CHA, CNA, and CMA joint statement entitled "Role of the Registered Nurse in Acute Cardiac Care."

#### *D. Other Issues as Developed*

1. To ensure accuracy, an observer should record the chronology of arrest events, and such a record should be reviewed by all individuals involved in the cardiac arrest prior to making entries in the medical record.

### SECTION V—REQUIREMENTS FOR ASSISTANTS IN SURGERY AND SURGICAL PRIVILEGES

#### *A. Surgical Privileges*

1. Initial assignment of surgical privileges may be on a provisional basis.

2. The assignment of provisional surgical privileges should be based upon a thorough review of all available documentary evidence concerning the applicant and his proficiency in performing particular surgical procedures.

3. Surgical privileges should remain provisional until the surgeon's competence can be demonstrated by observation to the satisfaction of the appropriate Medical Staff Committee or its designates.

4. The surgical privileges of each staff member should be subject to the review of an appropriate committee of the medical staff at appropriate intervals (at least annually).

5. Medical staffs in hospitals without qualified medical personnel to conduct a periodic review of surgical privileges should consider requesting and obtaining assistance from outside the medical staff or community.

6. The surgical privileges designated for each staff physician should be in writing and be available to operating room supervisors.

7. Operating room supervisors, in each hospital, should become familiar with the medical staff lists of surgical privileges and the criteria for the

use of assistants, and, when possible, they should call to the attention of the Chief of Service, or his designate, any current or anticipated deviation from such criteria, as soon as possible, for appropriate and immediate action.

8. All surgical procedures performed by physicians with provisional surgical privileges should be observed by senior staff surgeons.

#### *B. The Physician Surgical Assistant*

1. Medical staffs should promulgate criteria which would assist in the determination of when a surgical assistant is, or is not, required. Such criteria should be in a form easily understood and interpreted by the hospital operating room supervisor.

2. Medical staffs should formulate criteria, and enforce regulations based thereupon, regarding qualifications of surgical assistants.

3. A physician should not be qualified as an assistant based solely upon a referral or on his position as an intern or resident.

4. Medical staffs within any given area (i.e. county, or group of counties in a rural area) may jointly determine a common classification of procedures which require an assistant in surgery.

#### *C. Other Personnel in Surgery*

1. The appropriate committee of the medical staff should identify those surgical procedures, by classification, for which current hospital operating room personnel may possess insufficient training or experience. For such procedures staff members may be individually authorized, by the hospital and by the appropriate Medical Staff Committee, to utilize their own respective personnel; provided however, any person so utilized should be a licensed nurse or should have completed a formal approved course of instruction in the technique to be employed.

2. A hospital and the appropriate committee of its medical staff may establish a policy whereby personnel other than registered nurses may be authorized to perform specific duties in the operating room, provided however, such personnel should at all times be responsible to a registered nurse who should be physically present in the operating room area.

#### *D. Other Issues as Developed*

1. As a concept, in areas where, because of the size of hospitals and medical staffs, effective review



of surgical privileges, education and discipline is sometimes difficult or inconsistent, coordinating committees composed of several medical staffs, and/or if desirable, medical societies, may be organized for assistance.

## SECTION VI—INFECTION CONTROL

### *A. The Infection Control Plan*

1. Each hospital and its medical staff should establish an Infection Control Committee.

2. The Infection Control Committee should have sufficient hospital and medical staff representation so as to assure the effective implementation and administration of the recommendations contained herein.

3. The Infection Control Committee should assume responsibility for the development, implementation and general supervision of a program for infection prevention, recognition and control.

### *B. Aseptic Technique*

1. Nursing personnel should report any breach of aseptic technique to appropriate nursing supervisors.

2. The nursing supervisor should notify the offender of the existence of this report and transmit a written report of the incident to the Infection Control Committee, with a copy to the medical chief of the service in which the violation occurred.

3. Medical staff bylaws should include rules and regulations which require appropriate disciplinary action for chronic offenders.

### *C. Infections in Patients*

1. The Infection Control Committee should establish specific criteria for the identification and reporting of infections existing in patients.

2. Attending physicians, in accordance with the criteria established, should identify and report immediately the existence of an infection in any of his patients.

3. Nursing personnel, in accordance with the established criteria, should report infections which come to their attention.

4. All infection reports, whether made by a physician or nurse, should be properly documented in writing and transmitted directly to the Infection Control Committee, or its designate. Such reports should not be made a part of the hospital record.

5. Once an infection shall have been identified,

its treatment should be the responsibility of the attending physician.

6. If the attending physician does not assume such responsibility, treatment should become the responsibility of the Infection Control Committee.

7. If a patient is admitted to one hospital with a postoperative infection possibly acquired at another hospital, the receiving hospital should immediately notify the original hospital.

8. If an infection is known or suspected, a culture should be ordered, preferably by the attending physician.

### *D. Infections in Medical and Hospital Personnel*

1. The medical staff, or an appropriate committee thereof, should establish specific criteria for the identification and reporting of infections existing on the persons of staff physicians and hospital employees.

2. Each physician and each hospital employee, in accordance with the criteria established, should identify and report immediately the existence of any infection on his person.

3. If a physician or hospital employee fails to identify and report the existence of such an infection, it should be the responsibility of persons designated by the hospital and medical staff or Infection Control Committee to assure that a report is made.

## SECTION VII—MATERNAL AND NEONATAL INJURIES

### *A. Pre-delivery*

1. Oxytocic drugs should be administered to undelivered patients only upon written order of the physician in charge of the patient.

2. Induction and/or stimulation of labor with I.V. oxytocic drugs should be initiated by a physician, who should remain at the bedside until he has been able to assess the reaction of the patient and her response has stabilized.

3. The observation of undelivered patients who have received, or are receiving, intravenous oxytocic drugs should not be assumed solely by nurses. A physician should be in constant attendance or immediately available in the labor room area. Should he leave, the oxytocic should be stopped until he returns.

4. The medical staff should determine whether or not intramuscular or buccal oxytocic drugs may be used in the hospital.



5. If the use of intramuscular oxytocic drugs is permitted by the medical staff, such drugs might be given by nurses, if the physician is physically present, or immediately available, in the labor room area. Ordinarily, when used, the medication should be diluted not less than 1:10, and if the medication is to be repeated, it should be given not less than 20 to 30 minutes apart in increments of not more than ¼ cc.

6. If the use of buccal oxytocic drugs is permitted by the medical staff, such drugs might be given by nurses, if the physician is physically present, or immediately available, in the labor room area.

7. Oxytocic solution in a nasal spray should be avoided during pregnancy.

8. During the first stage of labor, nursing should monitor fetal heart tones at least every 30 minutes (or, more frequently, if any abnormalities are noted). Quality, rate and regularity of fetal heart tones should be recorded in each instance.

9. During the second stage of labor, fetal heart tones should be so monitored and recorded every five minutes (or, more frequently, if any abnormalities are noted).

10. During the first stage of labor, maternal blood pressure and pulse should be taken and recorded hourly (or, more frequently, if any abnormalities are noted).

11. During the second stage of labor, nurses should observe and record blood pressure and pulse at ten minute intervals until an anesthesia record is started. Until an anesthetist is present, nursing should continue to monitor vital signs.

12. Each medical staff should establish a policy for screening antibodies as an integral part of antepartum care.

13. The attending physician should give the orders for an obstetrical patient upon, or after, her admission to the maternity suite. Antepartum standing orders for medication should not be permitted.

14. When feasible, the attending physician should assure that his obstetrical patient is pre-registered at the hospital, prior to her admittance for delivery. Additionally, when feasible, the attending physician should assure that, by the eighth month of pregnancy, the hospital has received a resume of previous obstetrical history, a current history and physical, and information regarding her blood type.

## *B. Delivery*

1. When delivery is imminent and the attending physician is not present and cannot be reached, nursing should contact the OB Supervisor who in turn should call the Chief of Service, a designated consultant, or the Chief of Staff immediately. Such reporting should be noted in the nurses' notes.

2. If a serious question arises regarding an order or procedure, nursing should contact the OB Supervisor who in turn should call the Chief of Service, a designated consultant, or the Chief of Staff immediately. Such reporting should be noted in the nurses' notes.

3. Nursing should continue its delivery responsibilities in the event no physician is present or immediately available. Delivery should not be intentionally delayed.

4. Each medical staff should consider establishing a policy for intravenous infusion on each delivery obstetrical patient until completion of delivery.

5. During the performance of a caesarian section procedure, there should be a physician in attendance whose only responsibility is to the infant.

6. Each medical staff should establish a policy for obtaining cord blood specimens for hemoglobin, Rh type and Coombs test.

## *C. Postpartum*

1. The patient should remain under the observation of the physician at least until bleeding, if any, has been controlled; and, of the nursing staff, until her vital signs have stabilized.

2. Generally, postpartum standing orders are not desirable.

## *D. The Newborn*

1. Specifically designated facilities should be provided for the care of premature infants.

2. Newborn infants should remain isolated from personnel not assigned to their care and feeding, and from visitors except where "rooming-in" is practiced.

3. Each infant should be marked for identification before removal from the delivery room.

4. Prophylaxis should be administered in the eyes of the newborn in accordance with Chapter 4, Subchapter 1, Section 2560, Title 17, California Administrative Code.

5. Oxygen monitoring and recording of the newborn should be done by nurses at least every two hours, and the precise volume percent should be recorded by nursing personnel at each stated interval.

6. The doctor's orders for percentage of oxygen concentration might be exceeded if deemed necessary by the nurse, and the nurse's notes should reflect the reason for, the variation and duration of, such additional concentration.

7. The attending physician should be notified of any deviation from ordered percentage of oxygen concentration as soon as possible and the record should reflect the fact of notification.

8. Oxygen monitoring equipment should be calibrated as often as is necessary to assure accuracy.

9. Nursery nursing personnel should be alerted to the potential of hemolytic disease by some positive means (preferably in writing) in the newborn chart when the newborn is brought to the nursery.

10. There should be continuing close observation by nursery nursing personnel, and any question of jaundice should be reported to the attending physician immediately and recorded in the nurse's notes as having been observed and reported.

11. The hospital should assure the availability of Rh<sub>0</sub> (D) Immune Globulin (human). Physician and hospital should assure that this biologic is offered when indicated, and each refusal to accept such treatment should be documented in writing.

12. When feasible, the delivering physician should notify the physician who will have responsibility for the newborn infant (if other than himself), prior to the delivery of the infant.

13. The delivering physician should be continuously responsible for the newborn infant until such time, if any, as another physician arrives to assume personal responsibility; and, any transfer of responsibility should be noted both in the maternal and newborn nursing notes.

14. Each medical staff should establish a policy for the identification and reporting of infections in the nursery.

#### *E. Other Issues as Developed*

1. The medical staff, or the appropriate designated committee thereof, should develop and maintain a continuing education program for all

registered nurses and licensed vocational nurses staffing the maternity unit.

2. Each medical staff should consider establishing criteria regarding obstetrical privileges and obstetrical consultations.

## SECTION VIII — INJECTION INJURIES

### *A. General*

1. The medical staff should survey the necessity of utilizing the method of injection as the route of administration of various drugs.

2. The medical staff, or an appropriate designated committee thereof, should review the utilization of blood transfusions.

### *B. Injection*

1. Nursing administration should initially, and at periodic intervals thereafter, conduct an evaluation of the injection technique of each hospital employee performing injections in the hospital.

2. The personal file of each employee who performs injections in the hospital should be documented with a current evaluation based upon demonstration(s) of injection technique. And noted deficiencies should be immediately rectified by appropriate in-service training.

3. The hospital and medical staff should establish criteria for monitoring intravenous infusion therapy and for recording observations made thereof.

4. The hospital and medical staff should identify those drugs most capable of producing injuries, and should conduct appropriate nursing in-service education concerning such drugs.

5. The hospital and medical staff should determine which drugs may be administered by nursing personnel, according to route of administration and to nursing personnel classification.

6. Nursing personnel shall document on the patient's chart the manner and exact site at which each injection was administered.

### *C. Post-Injection*

1. Nursing personnel should report all complications or unusual occurrences, after injections, to supervisory nursing personnel, and such a report may be recorded in the nursing notes. Upon notification, supervisory nursing personnel should immediately notify the attending physician.



# LETTERS to the Editor

## Gonorrhea and Ophthalmia Prophylaxis

BOTH LOCALLY AND nationally there has been a horrendous increase in gonorrhea, as reported to health authorities, and this reporting almost certainly reflects much less than the actual incidence.

It may be assumed that, in the population most frequently involved, many infected mothers may not know they are infected, do not usually seek medical care, are frequently pregnant, do not always receive prenatal care; and labor, delivery, and the care of the neonate may be much less than optimal. The numerous reports pointing out this tremendous incidence suggest that exposure of the neonate to gonorrhea may be a frequent event.

Why then is the reporting of ophthalmia of the newborn at such a low level with no corresponding increase during the very period of widespread gonorrheal infection. In California reported cases are only about two per month, although conscientious reporting of this condition, which threatens vision and was once the leading cause of blindness, might be expected. There have been similar comments elsewhere in recent months.

What has happened to conjunctivitis of the newborn? It is simply unreported? Does the use of silver nitrate drops or penicillin prevent its occurrence? Is it likely that a single administration of either agent should be so unfailingly effective? It can certainly be suspected that prophylaxis is frequently applied indifferently and not constantly, probably often not at all in the population principally involved.

Except for some mysterious reason there should be an increase in newborn ophthalmia to correspond to this epidemic incidence. Note that Crede originally encountered an incidence exceeding 10 percent of all newborns. Crede insisted that prophylaxis with silver nitrate weaker than 2 percent

was unreliable; today we rely entirely on 1 percent solution. It is certainly improbable that a single transient exposure to penicillin would be completely effective in preventing this infection.

There are many who are distrustful of the forms of prophylaxis in current use and who object to the trauma and the mechanical and chemical conjunctivitis which ensues if prophylaxis is done conscientiously. If all babies were dismissed from the hospital with strict warnings to the mother that *any* ocular discharge is an emergency which should promptly be brought to medical attention, this should result in early diagnosis; and penicillin should be curative practically overnight. At least this should be completely effective in that portion of the population which can be relied upon to seek medical advice promptly—prophylaxis, for whatever it is worth, being reserved for those who may be expected to escape further attention.

EDWARD B. SHAW, M.D.

*Professor of Pediatrics, Emeritus  
School of Medicine, University  
of California, San Francisco  
Medical Center*

## White House Conference On Nutrition

*To the Editor:* [Washington, D.C., December 4, 1969] President Nixon's White House Conference on Food, Nutrition and Health ended today with little evidence that any significant number of the Conference participants understand the problems of starvation and malnutrition in the affluent United States. There was even less evidence that they know what to do to correct it. Human starvation and malnutrition in this advanced industrial nation are still regarded as mythical by most of the middle-class representatives of the academic and business worlds. The small group of "community representatives," invited to lend some air of "democracy" to the sordid affair, made ineffectual efforts to arouse some sense of urgency in the obviously middle-class leaders of the Conference.



The Welfare Rights people, the National Council of Negro Women, the militant Mexican-American Raza people and such liberal celebrities as Walter Reuther and Ralph Abernathy laid down a verbal barrage which obviously failed to penetrate the smug class attitudes of the medical and nutrition "experts" and the exploiters from Pepsi-Cola, Coca-Cola, General Foods Corporation and other representatives of the private food and snack industry.

In my own rather narrow field of interest, human pregnancy nutrition, total chaos prevailed:

1. The special nutritional stress of pregnancy was *not* recognized by members of the Conference panel concerned with nutrition problems of pregnant women, infants and children.

2. The special nutritional problems of our pregnant teenage girls in poverty were not recognized. The primary emphasis of the panel in discussion of teenage pregnancy was placed on *birth control* and *abortion*. The roles of the private soft drink, snack and cigarette industries in teenage malnutrition were *not* examined.

3. The role of starvation and malnutrition in maintaining high infant mortality and the high incidence of low birth weight infants in the U.S.A. poverty areas was *not* recognized.

4. The common nutritional diseases of human pregnancy were not recognized.

5. The total lack of any national *nutrition standards* for the pregnant woman and her unborn fetus was not recognized and no efforts were made to establish such standards.

6. The widespread unscientific clinical nutrition practices established in our public prenatal clinics serving the poor were *not* recognized: inadequate low calorie, low sodium diets, diuretics ("water pills"), amphetamines (Dexidrene®, "speed"), a variety of drug-company sponsored dietary supplements, salt substitutes. This is the present irrational approach of U.S. medicine to the special nutritional stresses of the so-called "low income, high risk prenatal patients."

Throughout this three-day meeting there has been the generally prevailing attitude among the health professionals that nothing is really known about these problems and that the real need is for "more research on hunger and malnutrition among the poor." In the field of human pregnancy nutrition this call for "more research" is the result of rigid class and racial prejudices because the needed research has already been done over the past 40 years by medical researchers here and throughout the world. One urgent need is *to apply*

scientific nutrition in human prenatal care. Another urgent need is to stop exploitation of human pregnancy nutrition by the U.S. private drug, soft drink, snack and cigarette industries. The White House Conference on Food, Nutrition and Health, December 2, 3 and 4, 1969, has been unable to define these problems of our people in poverty and ignorance and hence will be unable to respond to these needs.

The only hope lies in the American people themselves who must in order to solve these deepening problems of unmet human need create new institutions. We must cast off the chains of blind traditions and economic greed which keep our people trapped in poverty and preventable diseases. An obvious and painful lesson from this White House Conference is that we cannot depend upon the present economic system to correct the human abuses and injustices which are the direct result of the system. A nation governed by millionaires cannot feed its starving women and children without removing these millionaires from political power. Let all humane American citizens consider these serious problems which grow more severe with each passing day.

TOM BREWER, M.D.  
Richmond, California

*Dr. Brewer was invited to the White House Conference on Food, Nutrition and Health.—Editor*

## Female of the M.D. Species

*To the Editor:* The paper by Drs. McGann, Alexander, and Fox, "Chromosomal Abnormality in a Child" (CALIFORNIA MEDICINE 112:30, January, 1970), went a long way towards explaining why there exists such a dearth of female MD's in California. To quote from the paper: "As a general rule, the degree of physical abnormalities and mental retardation increases as the number of x-chromosomes increases."

I admire these doctors for making public their findings in an area of research that still, even after generations of always reaching the same inescapable conclusion of male superiority, affords some measure of contemporary controversy. *Caveat sic.*

JOHN ZILIUS, B.S.  
Second Year Medical Student,  
University of California, San  
Diego, School of Medicine

## ***Information***

### **Newer Concepts of the Evaluation of Cardiac Function**

**WILLIAM W. PARMLEY, M.D., AND  
EDMUND H. SONNENBLICK, M.D.**

*Material Supplied by the California Heart Association*

IN DEALING WITH the diseased heart, the clinician must make two important judgments. First, the underlying cause of the disease and associated anatomic defects must be determined, and second, the functional consequences of the lesion must be assessed. Although this latter judgment can often be made by a careful history and physical examination, or by imposing a stress such as mild exercise, it is often necessary to make more precise physiologic measurements of cardiac function, which are best obtained during diagnostic cardiac catheterization. This article will briefly discuss some aspects of the cardiac evaluation obtained during catheterization which deal both with the function of the heart as a pump and with the contractile properties of the heart muscle itself. In particular, it is necessary to evaluate to what extent an anatomically correctable defect is causing abnormal loading and "pump" failure and to what degree a depression of cardiac muscle function itself has occurred.

The primary function of the heart is to maintain an adequate cardiac output appropriate to the changing energy requirements of the body. The cardiac output, which is determined by peripheral metabolic needs and return of venous blood, is the product of heart rate and stroke volume. The stroke volume of the ventricle, in turn, is influenced

by three factors: (1) the preload or end diastolic volume, (2) the afterload or pressure level which must be reached in order to eject blood into the aorta, and (3) the contractile state or "vigor of contraction" of the heart muscle.

The stroke volume of the heart is adjusted *beat to beat* by changes in preload or end diastolic volume. Thus as the filling pressure and diastolic volume of the ventricle are augmented, the stroke volume increases, while the fraction of blood ejected by the ventricle remains relatively constant. This increase in stroke volume resulting from increments in end-diastolic is known as Starling's law of the heart, and is a primary mechanism whereby cardiac output is altered on a beat to beat basis.

The second factor which influences stroke volume is the afterload. For example, from the same end diastolic volume, a marked increase in aortic pressure will reduce stroke volume, while a decrease in aortic pressure will increase stroke volume. The reduction in stroke volume in a given beat due to an increased afterload, leaves blood behind in the ventricle so that subsequent end diastolic volume will be larger. With this increase in end-diastolic volume, the stroke volume will go up and output will be restored.

The third factor which influences stroke volume is a change in the contractile state of the heart muscle. The contractile state, or contractility of the heart, reflects the vigor of contraction and is characterized by the speed and extent of contraction. Normally the contractility of the heart is increased by norepinephrine which is released reflexly from sympathetic nerve endings in the heart or from the adrenal glands and is carried by the blood stream to the heart. The increase in the extent of muscle shortening (which accompanies an increase in contractility) is manifest by an increase in stroke volume at the same end diastolic volume. Thus the fraction of blood ejected from the ventricle during each systole is augmented by an increase in the contractile state of the heart muscle.

In disease states, pump performance and muscle function may not be deranged simultaneously. Thus, in severe aortic stenosis, the imposed afterload may be of such a magnitude that pump performance is impaired despite relatively normal muscle function. Similarly in the presence of massive intracardiac or peripheral arteriovenous shunting of blood and markedly elevated cardiac

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outputs, congestive failure with massive fluid accumulation may ensue, although underlying myocardial function may be normal. It is essential to distinguish failure due to abnormal loading of the heart from that resulting from depression of muscle function per se.

The function of the heart muscle itself may best be analyzed in terms of the relationship between force development in the wall of the heart and the velocity of muscle shortening. This "force-velocity" relation is the most fundamental mechanical relationship of heart muscle and can be calculated from pressure and volume measurements obtained during catheterization. Although this cannot be routinely measured at present, current experimental studies suggest that it may become an integral part of future diagnostic catheterization studies. The value of this approach is that it provides a more precise measurement of muscle function aside from overall pump function of the heart which may be influenced by valvular defects or abnormal shunting.

Although a consideration of the above factors allows one to describe cardiac function as a whole, it has recently become clear that localized areas of heart muscle have altered function, particularly in patients with coronary artery disease. With cine ventriculograms obtained by the injection of radio-opaque dye into the left ventricle, regional abnormalities of contraction may be recognized. These include areas of the heart wall which do not move at all (akinesis), areas which contract poorly (hypokinesis), and areas which expand rather than contract (dyskinesis). In addition it is also clear that asynchrony of contraction of the entire heart may also influence cardiac function adversely.

Recent studies have also demonstrated that resting measurements of pump function during

cardiac catheterization may be essentially normal in the face of considerable disease of the myocardium. Thus it becomes important to elicit abnormal function by stressing the heart. This is commonly done by having the patient perform supine bicycle exercise, by the intravenous administration of a catecholamine such as Isuprel® or by increasing the heart rate with electrical pacing. Furthermore, abnormal function may also be elicited by increasing the afterload with angiotensin which increases arterial pressure but does not appreciably affect the contractile state of the heart itself. In patients with coronary artery disease, stress tests of the heart have been particularly useful in eliciting regional metabolic abnormalities (lactate production) as an indicator of regional hypoxia unassociated with angina pectoris. Such functional abnormalities have correlated well with the anatomic demonstration by coronary arteriography of occlusion or stenosis of a major vessel to that area of myocardium. The value of measurement made during stress testing of the heart, therefore, is that abnormalities may be induced which are indicative of limited cardiac reserve even though the function of the heart as a pump may appear normal at rest.

In summary, therefore, the pump function of the heart can be measured in terms of filling pressure (end diastolic volume) and stroke volume, while contraction properties of the heart muscle itself are measured by the "force-velocity" relation of the muscle. Furthermore, regional contraction abnormalities can be evaluated by the use of cine studies of the contracting left ventricle. A combination of the above studies can provide valuable information to the practitioner which is of considerable benefit in both the diagnosis and treatment of clinical heart disease.



# PUBLIC HEALTH REPORT

Louis F. Saylor, M.D., M.P.H., Director, State Department of Public Health

## Suicide Prevention— The Physician's Role

DO PHYSICIANS FAIL to recognize significant clues to suicide? If so, this would account for failure to forestall preventable deaths.

Suicide has been among the ten leading causes of death in California since 1910.<sup>1</sup> In 1968, it accounted for 3,427 deaths.<sup>2</sup> Unsuccessful attempts are sometimes estimated at seven to eight times the number of completed suicides and many who try once and survive, kill themselves later.

California's 1968 suicides ranged in age from under 20 to over 80, with 1,069 between the ages of 40 and 55. Particularly high rates are found in all age groups over 40. The major means were firearms and explosives, followed by drugs, including barbiturates and sleeping pills. Other agents and methods were poisons, gas, carbon monoxide, hanging, strangulation, drowning, cutting and piercing instruments, and jumping from high places.

Among the persons who kill themselves, often during the most productive years of their professional lives, are a significant number of physicians, and most commonly among them, psychiatrists. As early as 1903, the American medical profession noted its own high suicide rate.<sup>3</sup> Studies in the United States and Great Britain attest the continuing vulnerability of physicians, especially those under 50. In both nations, easy access to drugs and development of drug dependence are cited as contributory factors.<sup>4,5</sup>

Particularly poignant is the fact noted in one study that colleagues and wives of suicidal physicians desperately sought help from other physicians, friends and medical societies, but in vain. Yet physicians may be in a position to prevent such destructive acts.

The essence of prevention, according to a leading suicidologist, is in recognizing that the potential victim is "in balance" between his wishes to live and his wishes to die, and in throwing one's

efforts on the side of life.<sup>6</sup> Most suicidal persons give notice of their intention by previous attempts, by direct or indirect verbal clues ("I'm going to end it all," "You'd be better off without me") or by such actions as putting affairs in order, giving away prized possessions or even buying a casket. Any such prodromal clue is a cry for help and should never be dismissed.

A particularly high risk group of potential suicides are persons over 40 with depression. Alcoholics, especially if they live alone, if they are about to lose or have recently lost a loved one, as by separation, divorce or death, are in special danger. Persons who suffer from anxiety, agitation, psychosis or organic impairment are at risk. So are patients who fear impending hospitalization, who are scheduled for surgical operation, especially mutilative, or who have learned that they may have or do have a malignant disease.

Adolescents are often at risk when the stresses of puberty and oncoming adulthood are too great for them. Some factors in the lives of male adolescents that are associated with suicide in later life have been identified in one study as loss of father through death or marital separation before son's entrance into college; the father's belonging to the professional class; cigarette smoking in college; failure to graduate from college; and self-assessed characteristics of insomnia, worries, self-consciousness and mood swings.<sup>7</sup> Prolonged loss of sleep, ingestion of narcotics, sedatives, alcohol and hallucinogenic drugs may lead to loss of controls over self-destructive impulses.<sup>8</sup>

Undoubtedly, physicians succeed in preventing suicides, but they do have some failures. About half of all who kill themselves see a physician some time during the month before. On average, a physician sees six potentially suicidal patients each year, although rarely is the chief complaint as obvious as, "I'm thinking of killing myself."<sup>9</sup>

In one study of 175 consecutive suicides and 197 hospital admissions for attempted suicides in San Francisco, one of three killed himself with a drug available only on a physician's prescription and two out of five attempted to do so. The com-

plaints which brought the patients to the physician covered a wide range, but most often involved depression.<sup>10</sup>

Why do physicians sometimes fail to evaluate their patients' suicidal potential?

If physicians experience anxiety in dealing with suicide, it is difficult for them either to assess the patient's emotional state clearly or provide the emotional support the patient needs. A physician may fail to take preventive steps if his cultural attitudes toward suicide, professional pride and personal abhorrence make him deny to himself that this is imminent. And the greater the prestige of the patient, the more the physician may deny the possibility of suicide.<sup>11</sup>

Yet the non-psychiatric physician is increasingly involved in identifying and managing depressed and suicidal persons. To reduce suicides, physicians should develop an active casefinding approach, a kind of awareness with a view to modifying depressed suicidal states before they become critical. Patients do not usually reveal spontaneously that they are thinking of suicide, but the physician's tactful questioning readily elicits this information, especially where there is a good patient-doctor relationship. The physician should, therefore, routinely inquire about depressive and suicidal states and, if appropriate, lead up gradually to questions about suicide plans. Further steps in management depend on the particular patient and the physician, but should include emergency medical and psychological support, consultation and referral when indicated and frequent communication with patients while they are still suicidal.<sup>12,13</sup>

Sometimes physicians hesitate to talk of suicide to disturbed patients for fear of putting the idea into their minds. But in its experience the Suicide Prevention Center of Los Angeles has found no

evidence that such questions ever harmed patients.

Suicidology is a new and expanding field, linking medicine and the behavioral sciences. California has 25 percent of the nation's suicide prevention centers, including the outstanding Los Angeles center codirected by Norman Farberow, Ph.D. and Robert E. Litman, M.D., and staffed by a distinguished multidisciplinary team. This center carries out a broad program of evaluation, assessment, referral, training and research.

California's physicians may find it helpful to achieve good working relations with suicide prevention centers and other appropriate community service agencies, including police and fire departments and local poison centers.\*

But perhaps the most important qualities a physician needs are sensitivity and intuition in listening for and responding to desperate pleas for help, and a non-judgmental attitude in dealing with them.

\*A list of California's suicide prevention centers is available from the State Department of Public Health, Bureau of Health Education, 2151 Berkeley Way, Berkeley, Calif. 94704.

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# In Memoriam

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Persons wishing to do so may make contributions to the Physicians' Benevolence Fund to honor the memory of a member who has died. Members of the family will be notified that such a contribution has been made and the name of the donor will be supplied.

Checks should be addressed to Physicians' Benevolence Fund, Inc., California Medical Association, 693 Sutter Street, San Francisco, Ca. 94102.

✧

AVERETT, LEONARD, Los Angeles. Died 15 January 1970 in Los Angeles of cardiac arrest, aged 85. Graduate of the Medico-Chirurgical College of Philadelphia, 1911. Licensed in California in 1949. Doctor Averett was a retired member of the Los Angeles County Medical Association and the California Medical Association, and an associate member of the American Medical Association.

✧

BARNES, JAMES HARRISON, Glendale. Died 24 December 1969 in Glendale of cancer, aged 46. Graduate of the University of Southern California School of Medicine, Los Angeles, 1954. Licensed in California in 1954. Doctor Barnes was a member of the Los Angeles County Medical Association.

✧

BEAN, GLENN M., Hanford. Died 5 January 1970 in Hanford, aged 50. Graduate of the College of Medical Evangelists, Loma Linda-Los Angeles, 1945. Licensed in California in 1946. Doctor Bean was a member of the Kings County Medical Society.

✧

BOEHME, EARL J., Los Angeles. Died 29 December 1969 on board S.S. Hope at Tunis, North Africa, of heart disease, aged 60. Graduate of the University of Minnesota Medical School, Minneapolis, 1933. Licensed in California in 1946. Doctor Boehme was a member of the Los Angeles County Medical Association.

✧

BROWN, DEWEY F., San Jose. Died 13 January 1970 in San Jose, aged 71. Graduate of the University of Nebraska College of Medicine, Omaha, 1924. Licensed in California in 1928. Doctor Dewey was a retired member of the San Mateo County Medical Society and the California Medical Association, and an associate member of the American Medical Association.

✧

BRUNEMEIER, EDWARD H., Placentia. Died 30 December 1969 in Palm Springs, aged 85. Graduate of Rush Medical College, Chicago, 1916. Doctor Brunemeier was a retired member of the Orange County Medical Association and the California Medical Association, and an associate member of the American Medical Association.

ELLIS, FRANK MILO, Rolling Hills. Died 10 January 1970 in Los Angeles of heart disease, aged 47. Graduate of the University of Ottawa Faculty of Medicine, Ontario, 1954. Licensed in California in 1954. Doctor Ellis was a member of the Los Angeles County Medical Association.

✧

HORN, EUGENE AARON, Torrance. Died 30 December 1969 in Miami of pulmonary disease, aged 34. Graduate of Tufts University School of Medicine, Boston, 1960. Licensed in California in 1961. Doctor Horn was a member of the Los Angeles County Medical Association.

✧

ISHAM, CHARLES A., San Diego. Died 22 January 1970 in San Diego, aged 59. Graduate of University of California Medical School, Berkeley-San Francisco, 1940. Licensed in California in 1940. Doctor Isham was a member of the San Diego County Medical Society.

✧

KIRCHNER, HERBERT J., Los Angeles. Died 24 December 1969 in Los Angeles of heart disease, aged 65. Graduate of the University of Illinois College of Medicine, Chicago, 1929. Licensed in California in 1929. Doctor Kirchner was a member of the Los Angeles County Medical Association.

✧

KOSKY, ALFRED A., Santa Monica. Died 11 January 1970 in Los Angeles of heart disease, aged 69. Graduate of the College of Medical Evangelists, Loma Linda-Los Angeles, 1924. Licensed in California in 1924. Doctor Kosky was a member of the Los Angeles County medical Association.

✧

KUFFEL, MARK J., Long Beach. Died 9 January 1970 in Long Beach, aged 63. Graduate of The Creighton University School of Medicine, Omaha, 1936. Licensed in California in 1937. Doctor Kuffel was a member of the Los Angeles County Medical Association.

✧

LORENZEN, LEE H., Pleasant Hill. Died 21 December 1969 in Walnut Creek of coronary thrombosis due to coronary atherosclerosis, aged 55. Graduate of Tulane University School of Medicine, New Orleans, 1939. Licensed in California in 1947. Doctor Lorenzen was a member of the Alameda-Contra Costa Medical Association.

✧

MATHE', CHARLES PIERRE, San Francisco. Died 22 January 1970 in Belmont, aged 79. Graduate of the University of California Medical School, Berkeley-San Francisco, 1916. Licensed in California in 1916. Doctor Mathé was a retired member of the San Francisco Medical Society and the California Medical Association, and an associate member of the American Medical Association.



MCDUGALL, MATTHEW W., Long Beach. Died 31 December 1969 in Long Beach, aged 64. Graduate of the University of Kansas School of Medicine, Lawrence-Kansas City, 1929. Licensed in California in 1930. Doctor McDougall was a member of the Los Angeles County Medical Association.

✧

MCNEIL, WARREN T., Stockton. Died 2 January 1970 in Stockton, aged 86. Graduate of Cooper Medical College, San Francisco, 1912. Licensed in California in 1912. Doctor McNeil was a member of the San Joaquin County Medical Society.

✧

MILLER, FREDERIC Y., Yucaipa. Died 5 January 1970 in Yucaipa, aged 48. Graduate of the University of California School of Medicine, Berkeley-San Francisco, 1951. Licensed in California in 1951. Doctor Miller was a member of the San Bernardino County Medical Society.

✧

MORGAN, DAVID W., Pasadena. Died 25 December 1969 in Pasadena of coronary artery disease, aged 57. Graduate of the University of Southern California School of Medicine, Los Angeles, 1940. Licensed in California in 1940. Doctor Morgan was a member of the Los Angeles County Medical Association.

✧

MORTON, JOHN HAROLD, Los Angeles. Died 6 January 1970 in Washington, D.C., of heart disease, aged 62. Graduate of the University of Wisconsin Medical School, Madison, 1934. Licensed in California in 1946. Doctor Morton was an associate member of the Los Angeles County Medical Association.

✧

NICHOLSON, DANIEL, San Francisco. Died 26 January 1970 in San Francisco, aged 75. Graduate of University of Manitoba Faculty of Medicine, Winnipeg, 1919. Licensed in California in 1959. Doctor Nicholson was a member of the San Francisco Medical Society.

✧

O'BRIEN, GEORGE F., Berkeley. Died 3 January 1970 in Berkeley of carcinoma of the pancreas, aged 62. Graduate of Stanford University School of Medicine, Palo Alto-San Francisco, 1933. Licensed in California in 1933. Doctor O'Brien was an associate member of the Alameda-Contra Costa Medical Association.

✧

OSGOOD, ELLIS C., Los Angeles. Died 27 January 1970 in Santa Monica of coronary occlusion, aged 59. Graduate of University of Pennsylvania School of Medicine, Philadelphia, 1938. Licensed in California in 1944. Doctor Osgood was a member of the Los Angeles County Medical Association.

✧

POWERS, ROBERT A., Palo Alto. Died 11 January 1970 in Palo Alto, aged 76. Graduate of Hahnemann Medical College of the Pacific, San Francisco, 1917. Licensed in California in 1917. Doctor Powers was a retired member of the Santa Clara County Medical Society and the California Medical Association, and an associate member of the American Medical Association.

REITZ, MARVEN J., Newport Beach. Died 8 January 1970 in Newport Beach, aged 63. Graduate of College of Osteopathic Physicians and Surgeons, Los Angeles, 1939. Licensed in California in 1939. M.D. degree from California College of Medicine, 1962. Doctor Reitz was a member of the Orange County Medical Association.

✧

ROBERTS, MARVIN T., Oakland. Died 24 December 1969 in San Leandro of hepatic failure due to fatty dystrophy of liver, aged 47. Graduate of the University of Oklahoma School of Medicine, Oklahoma City, 1954. Licensed in California in 1955. Doctor Roberts was a member of the Alameda-Contra Costa Medical Association.

✧

SHUMAKER, PHIL W., Beverly Hills. Died 30 December 1969 in Santa Monica of perforated aorta valve, aged 66. Graduate of Stanford University School of Medicine, Palo Alto-San Francisco, 1930. Licensed in California in 1930. Doctor Shumaker was a member of the Los Angeles County Medical Association.

✧

VAN BUSKIRK, JAMES DALE, Los Angeles. Died 27 December 1969 in Los Angeles of heart disease, aged 88. Graduate of University Medical College of Kansas City, Missouri, 1906. Licensed in California in 1924. Doctor Van Buskirk was a retired member of the Los Angeles County Medical Association and the California Medical Association, and an associate member of the American Medical Association.

✧

WALLA, GRACE IRENE, Los Angeles. Died 20 November 1969 in Reno of diabetic coma, arteriosclerosis, aged 45. Graduate of the College of Medical Evangelists, Loma Linda-Los Angeles, 1950. Licensed in California in 1950. Doctor Walla was an associate member of the Los Angeles County Medical Association.

✧

WELCH, ELWYN H., Pomona. Died 6 January 1970 in Pomona of emphysema, aged 74. Graduate of the University of Minnesota Medical School, Minneapolis, 1923. Licensed in California in 1924. Doctor Welch was a member of the Los Angeles County Medical Association.

✧

WHALMAN, HAROLD F., Los Angeles. Died 28 December 1969 in Los Angeles of hypertensive cardiovascular disease, aged 70. Graduate of the University of California Medical School, Berkeley-San Francisco, 1928. Licensed in California in 1928. Doctor Whalman was a member of the Los Angeles County Medical Association.

✧

WIKE, PAUL W., Upper Lake. Died 8 December 1969 near Bishop in a plane crash, aged 33. Graduate of the University of Arkansas School of Medicine, Little Rock, 1964. Licensed in California in 1965. Doctor Wike was a member of the Mendocino-Lake County Medical Society.

✧

ZENER, FRANCIS B., Santa Barbara. Died 24 January 1970 in Santa Barbara, aged 69. Graduate of Washington University School of Medicine, St. Louis, 1925. Licensed in California in 1946. Doctor Zener was a member of the Santa Barbara County Medical Society.

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**host:** Fresno County Medical Society  
Samuel Ross, M.D., Regional Chairman

**guest speaker:** Sherrel L. Hammar, M.D., Associate Professor  
of Pediatrics and Director, Division of  
Adolescent Medicine, University of  
Washington, Seattle  
(made possible by a grant from  
Merck, Sharp & Dohme Postgraduate Program)

**institute fee:** \$20.00. For additional information contact:  
Continuing Medical Education  
California Medical Association  
693 Sutter Street, San Francisco 94102

All California Medical Association members and their families  
are cordially invited to attend.

# CONTINUING MEDICAL EDUCATION ACTIVITIES IN CALIFORNIA AND HAWAII (FORMERLY WHAT GOES ON)

## COMMITTEE ON CONTINUING MEDICAL EDUCATION

THIS BULLETIN of information regarding continuing education programs and meetings of various medical organizations in California and Hawaii is supplied by the Committee on Continuing Medical Education of the California Medical Association. In order that they may be listed here, please send communications relating to your future meetings or postgraduate courses to Committee on Continuing Medical Education, California Medical Association, 693 Sutter Street, San Francisco 94102; or phone: (415) 776-9400, extension 241.

## ALCOHOLISM AND DRUG USE

March 18—**Alcoholism.** Agnews State Hospital at Agnews State Hospital, San Jose. Wednesday. 1½ hrs. Contact: J. Elizabeth Jeffress, M.D., Agnews State Hospital, San Jose 95114. (408) 262-2100.

May 16 & 23—**The Drug Scene.** University of California Extension, Riverside, at 1500 Life Sciences Building, UC Riverside. Two Saturdays. Primarily for physicians. 14 hrs. Contact: Ray Olitt, Health Services Program Coordinator, UC Extension, Riverside 92502. (714) 787-4329.

## CANCER

May 15-16 — **Hormones and Neoplasms—Cancer Conference.** USC at Century Plaza Hotel, Los Angeles. Friday-Saturday. 12 hrs.

## COMMUNITY MEDICINE

March 23-26—**The Urban Scene.** American Orthopsychiatric Association at Mark Hopkins and Fairmont Hotels, San Francisco. Monday-Thursday. Delivery of health care services, racism, hunger, dilemmas in welfare and education, law and order, long range urban planning, children designated delinquents, black adolescents, perinatal factors and development, natural history of brain dysfunction, psychological considerations of transplants in children. \$25 for non-members. Contact: Marion F. Langer, Ph.D., AOA, 1790 Broadway, New York 10019. (212) 586-5690.

## MEDICINE

March 26—**Obesity.** USC at Hilton Hotel, Los Angeles. Thursday. Recent advances in fat metabolism and behavioral research, feeding habits, management of obesity control. 6 hrs. \$30.

April 2-3—**California Thoracic Society—Annual Meeting Scientific Sessions.** Hilton Hotel, San Francisco. Thursday-Friday. New diagnostic techniques in pulmonary disease, TB and other lung infections, young investigators session, the air pollution chain, respiratory care. 12 hrs. Contact: Miss Elma Plappert, Exec. Sec., CTS, 424 Pendleton Way, Oakland 94621. (415) 636-1756.

April 3-4 — **Arrhythmias in Clinical Practice.** Sacramento-Yolo-Sierra Heart Association at Sacramento Inn, Sacramento. Friday-Saturday. Relevant anatomy and physiology, pharmacology, clinical recognition and treatment of rhythm disturbances of the heart. \$15. 10 hrs. Contact: Harold M. Lowe, M.D., Chairman, Symposium Committee, Sacramento-Yolo-Sierra Heart Assoc., Dept. of Cardiovascular-Pulmonary Diseases, Mercy Hospital, 4001 J Street, Sacramento 95819. (916) 456-7881.

## KEY TO ABBREVIATIONS AND SYMBOLS

Medical Centers and CMA Contacts  
for Information

- CMA:** California Medical Association  
Contact: Continuing Medical Education, California Medical Association, 693 Sutter Street, San Francisco 94102. (415) 776-9400, ext. 241.
- LLU:** Loma Linda University  
Contact: John E. Peterson, M.D., Associate Dean for Research Affairs, Loma Linda University School of Medicine, Loma Linda 92354. (714) 796-7311.
- PMC:** Pacific Medical Center  
Contact: Arthur Selzer, M.D., Chairman, Education Committee, Pacific Medical Center, Clay and Webster Streets, San Francisco 94115. (415) 931-8000.
- STAN:** Stanford University  
Contact: Thomas A. Gonda, M.D., Associate Dean, Stanford University School of Medicine, 300 Pasteur Drive, Stanford 94305. (415) 321-1200, ext. 5371.
- UCD:** University of California, Davis  
Contact: George H. Lowrey, M.D., Professor and Chairman, Department of Postgraduate Medicine, University of California, Davis, School of Medicine, Davis 95616. (916) 752-0831.
- UCI:** University of California—California College of Medicine, Irvine  
Contact: Robert Combs, M.D., Associate Dean, University of California, Irvine—California College of Medicine, Irvine 92664. (714) 833-6991.
- UCLA:** University of California, Los Angeles  
Contact: Donald Brayton, M.D., Associate Dean and Head, Continuing Education in Medicine and the Health Sciences, 15-39 Rehabilitation Center, UCLA Center for the Health Sciences, Los Angeles 90024. (213) 825-6514.
- UCSD:** University of California, San Diego  
Contact: Michael Shimkin, M.D., Associate Dean for Health Manpower, 1809 Basic Sciences Building, University of California, San Diego, School of Medicine, La Jolla 92038. (714) 453-2000, ext. 2704.
- UCSF:** University of California, San Francisco  
Contact: Seymour M. Farber, M.D., Dean, Educational Services and Director, Continuing Education, Health Sciences, University of California Medical Center, San Francisco 94122. (415) 666-1692.
- USC:** University of Southern California  
Contact: Phil R. Manning, M.D., Associate Dean, Postgraduate Division, University of Southern California School of Medicine, 2025 Zonal Avenue, Los Angeles 90033. (213) 225-1511, ext. 203.



April 3-5—**Sixth Annual Symposium—San Diego Society of Internal Medicine.** Warner Springs Resort, San Diego County. Friday-Sunday. Pulmonary Disease. \$15. 12 hrs. Contact: Thomas J. Lehar, M.D., Program Chairman, 6th Annual Symposium, 2001 Fourth Ave., San Diego 92101. (714) 234-6261.

April 6-15—**Cardiology for the Consultant—A Clinician's Retreat.** American College of Cardiology at Rancho Santa Fe Inn, Rancho Santa Fe. Ten day program for well-trained clinicians to sharpen ability in the field of cardiology. 52 hrs. Contact: William D. Nelligan, Exec. Dir., ACC, 9650 Rockville Pike, Bethesda, Md. 20014. (301) 530-1600.

April 6-17—**Coronary Care Unit Program for Physicians.** CRMP Area V at Los Angeles County-USC Medical Center. Two week course repeated monthly through June, 1970. Arrhythmia detection, diagnosis and therapy, defibrillation and cardioversion, central venous pressure monitors, placement of pacing catheters, new aspects in diagnosis and treatment of congestive heart failure, shock and associated respiratory problems, and CCU management in community hospitals. Contact: Gladys Ancrum, Dr. P. H., Administrative Associate, CRMP Area V, 1 West Bay State St., Alhambra 91801. (213) 576-1626.

April 8—**18th Annual Physicians Cardiovascular Symposium.** Central Valley Heart Association at Fresno Travel Host, Fresno. Wednesday. Premature Coronary Atherosclerosis, Angina Pectoris, Arrhythmias Accompanying Acute Myocardial Infarction, Hyperlemic Patient, Cardiac Auscultation in Pregnancy, Effect of Pharmacological Agents and Postural Changes on Heart Murmurs, Valvular Heart Disease Surgery, Digitalis Glycosides. \$20. 7 hrs. Contact: Frances Cuthbertson, Exec. Dir., CVHA, 1759 Fulton Street, Fresno 93721. (209) 237-0288.

April 8-9—**Medical Surgical Gastroenterology.** USC at Hilton Hotel, Los Angeles. Wednesday-Thursday. 12 hrs.

April 10—**Annual Symposium on Heart Disease.** Orange County Heart Association at Disneyland Hotel, Anaheim. Friday. Contact: Liggett McLaws, Program Dir., OCHA, P.O. Box 1704, Santa Ana 92702. (714) 947-3001.

April 10 — **13th Annual Physicians Symposium on Heart Disease.** Santa Clara County Heart Association at San Jose Hyatt House, San Jose. Friday. \$15. 6 hrs. Contact: William G. Allayaud, Exec. Dir., SCCHA, 1984 The Alameda, San Jose 95126. (408) 248-1517.

April 11—**Myocardial Infarction.** PMC. Saturday. Principles and techniques in a coronary care unit, electrocardiographic diagnosis, therapeutic approach to arrhythmias, heart failure in myocardial infarction, cardiac rehabilitation and the value of exercise, anticoagulation. \$35. 8 hrs.

April 22-25—**Advances in Endocrinology and Metabolism.** UCSF. Wednesday-Saturday. Intensive review of interrelationships between metabolic disease and endocrine dysfunction, critical evaluation of new developments.

May 4-15—**Coronary Care Unit Program for Physicians.** CRMP Area V. See Medicine, April 6-17.

May 4-22—**Coronary Care for Physicians Training Program.** CRMP Area IV and Cedars-Sinai Medical

Center at Cedars of Lebanon Hospital, Los Angeles. Three week course repeated six times through November, designed for practicing internists or cardiologists who will subsequently be working in or directing CCU in community hospitals. Electrocardiography, physical diagnosis, CCU planning and administration, electrolytes and acid-base metabolism, emphasis on practical techniques. Contact: Herbert Stein, M.D., Coronary Care for Physicians Training Programs, Dept. of Cardiology, Cedars of Lebanon Hospital, Box 54265, Los Angeles 90029. (213) 662-9111, ext. 306.

May 9—**Symposium on Clinical Pharmacology and Drug Therapy.** Division of Clinical Pharmacology, Department of Medicine, STAN, and Palo Alto Medical Clinic at STAN. Saturday. \$15, no fee for medical students and house staff. Contact: Stanley N. Cohen, M.D., Room S-161, STAN. (415) 321-1200, ext. 6021.

May 9—**Disease of the Gastrointestinal Tract.** See Radiology—Pathology, May 9.

May 12—**Analytical Approach to Cardiac Diagnosis.** American College of Cardiology and LLU at LLU. Tuesday. Representative cases of heart disease: history, examination, laboratory and radiological procedures. 7 hrs. Contact: William D. Nelligan, Exec. Dir., ACC, 9650 Rockville Pike, Bethesda, Md. 20014. (301) 530-1600.

May 13-14—**Coronary Care.** USC at Hilton Hotel, Los Angeles. Wednesday-Thursday. 12 hrs.

May 15—**California Heart Association—Annual Meeting Scientific Sessions.** Hotel del Coronado, Coronado. Friday. Coronary thrombosis and myocardial infarction, problems in ECG diagnosis of myocardial infarction, premature coronary disease, coronary arteriography. \$10. 7 hrs. Contact: Rodman D. Starke, M.D., 1370 Mission St., San Francisco 94103. (415) 626-0123.

May 15-17—**Basic Principles of Cardiac Therapy.** PMC and the American College of Cardiology at Jack Tar Hotel, San Francisco. Friday-Sunday. Clarification of pathophysiological basis of various disease states, rational approach to drug usage. \$80 members, \$120 non-members. 24 hrs. Contact: PMC.

May 16-17—**The Stroke Patient.** Granada Hills Community Hospital and San Fernando Valley State College Health Sciences Department at Main Auditorium, Speech Building, San Fernando Valley State College, Los Angeles. Saturday-Sunday. \$10. 16 hrs. Contact: Arno A. Roscher, M.D., Program Chairman, Granada Hills Community Hospital, 10445 Balboa Blvd., Granada Hills 91344. (213) 360-1021.

May 22-23—**Instrumental Acquisition of Cardiological Data with Clinical Correlation.** American College of Cardiology, Memorial Hospital of Long Beach, and Long Beach Heart Association at Memorial Hospital of Long Beach. Friday-Saturday. \$55. 14 hrs. Contact: William D. Nelligan, Exec. Dir., ACC, 9650 Rockville Pike, Bethesda, Md. 20014. (301) 530-1600.

May 25-28—**International Conference on Vascular Diseases of the Brain and Spinal Cord.** American Academy of Neurology, USC and Rancho Los Amigos Hospital at Anaheim Convention Center, Anaheim. Monday-Thursday. U.S. and international papers, rehabilitation team personnel invited. Limited traineeships available. \$125. 18 hrs. Contact: Richard P.

Boggs, M.D., Chief, Division of Neurological Sciences, Rancho Los Amigos Hospital, 7601 E. Imperial Highway, Downey 90242. (213) 869-0921.

June 1-12—**Coronary Care Unit Program for Physicians.** CRMP Area V. See Medicine, April 6-17.

June 5-6—**Vectorcardiography.** UCSF. Friday-Saturday.

June 15-July 3—**Coronary Care for Physicians Training Program.** CRMP Area IV. See Medicine, May 4-22.

Continuously—**Basic Home Course in Electrocardiography.** One year postgraduate series, ECG interpretation by mail. Physicians may register at any time. \$100 (52 issues). Contact: USC.

Continuously—**Training in the Procedure of Tonometry.** Northern California Society for the Prevention of Blindness at the Glaucoma Screening Clinic, San Francisco. Weekly Saturday morning program in tonometry for internists and general practitioners. Advance appointment required, no charge. 3 hrs. Contact: Frederic S. Weisenheimer, Ed.D., Exec. Dir., NCSBP, 4200 California Street, San Francisco 94118. (415) 387-0934.

### Grand Rounds—Medicine

#### Tuesdays

8:30-10:00 a.m., Assembly Hall, Harbor General Hospital, Torrance. UCLA.

#### Wednesdays

10:30-12:00 noon. Auditorium, Medical Sciences Building. UCSF.

11:00 a.m., Room 1645, Los Angeles County-USC Medical Center. USC.

12:30 p.m., Auditorium, School of Nursing, Orange County Medical Center. UCI.

12:30-1:30 p.m., University Hospital, UCSD.

#### Thursdays

10:30-12:00 noon, Room 33-105, UCLA Medical Center. UCLA.

#### Fridays

8:00 a.m., Courtroom, Third Floor, Kern County General Hospital, Bakersfield. CRMP Area IV.

8:30 a.m., Auditorium, Lebanon Hall, Cedars of Lebanon Hospital, Los Angeles. CRMP Area IV.

Neurology. 10:15 a.m., held alternately at Stanford University Hospital and Neurology Conference Building 7, V.A. Hospital, Palo Alto. STAN.

1st and 3rd Fridays, 11:00 a.m., Auditorium, Brown Building, Mount Sinai Hospital, Los Angeles. CRMP Area IV.

1:15 p.m., Lieb Amphitheater, Timken-Sturgis Research Bldg., La Jolla. Scripps Clinic and Research Foundation.

Rheumatology Grand Rounds. 11:45 a.m., Room 6441, Los Angeles County-USC Medical Center, Los Angeles. USC.

### MENTAL RETARDATION

May 22-23—**The Mentally Retarded Adult in the Community.** UCSF. Friday-Saturday.

June 8-19—**Mental Retardation.** UCLA and Pacific State Hospital, Pomona, at UCLA Neuropsychiatric Institute. Two weeks. For physicians and allied profession-

als. Causation, symptomatology, care, treatment and management, diagnostic techniques suitable for office practice, parental reactions and intra-family psychopathology, recent research findings. 80 hrs. Contact: UCLA.

### OBSTETRICS AND GYNECOLOGY

May 2-3—**Female Urology.** Tri-County Obstetrical and Gynecological Society at Santa Barbara Biltmore Hotel, Santa Barbara. Saturday-Sunday. 10 hrs. Contact: Jack R. Robertson, M.D., 1430 E. Main St., Suite 202, Santa Maria 93454. (805) 925-8759.

May 15-16—**Obstetrics and Gynecology Symposium.** Southern California Permanente Medical Group and Kaiser Foundation Hospitals at Beverly Hilton Hotel, Beverly Hills. Friday-Saturday. Contact: Shirley Gach, Rm. 6014, So. Calif. Permanente Med. Group, 4900 Sunset Blvd., Los Angeles 90027. (213) 663-8411.

### Grand Rounds—Obstetrics and Gynecology

#### Mondays

10-11:30 a.m., Assembly Room, First Floor, Harbor General Hospital, Torrance. UCLA.

#### Fridays

8 a.m., Auditorium, Orange County Medical Center. UCI.

### PEDIATRICS

March 20-21—**Pulmonary Disease in Newborns.** UCI, CRMP Area VIII in cooperation with the National Cystic Fibrosis Research Foundation at Childrens Hospital of Orange County. Friday-Saturday. Registration by March 1 is necessary. 8½ hrs. Contact: Bruce D. Ackerman, M.D., Dept. of Pediatrics, UCI.

April 3-4—**Pediatric Symposium—Nephrology.** Southern California Permanente Medical Group and Kaiser Foundation Hospitals at Ambassador Hotel, Los Angeles. Friday-Saturday. Contact: Shirley Gach, Rm. 6014, So. Calif. Permanente Med. Group, 4900 Sunset Blvd., Los Angeles 90027. (213) 663-8411.

April 4-5—**Armchair Allergy.** PMC at International Inn, San Francisco. Saturday-Sunday. Early diagnosis, role of steroids in management of asthma, skin tests, current concept of the basic steps in the allergic reaction. \$50. 14 hrs.

April 18—**Infectious Diseases.** UCSF at Childrens Hospital, San Francisco. Saturday. For pediatricians, family physicians, internists and clinically oriented bacteriologists. 5½ hrs.

April 22-25—**The Hospitalized Child, His Family and His Community.** American Association for Child Care in the Hospital, Stanford Childrens Convalescent Hospital, UCSF and STAN at Sheraton-Palace Hotel, San Francisco. Wednesday-Saturday. 15 hrs. Contact: Helen H. Glaser, M.D., Stanford Childrens Convalescent Hospital, 520 Willow Road, Palo Alto 94304. (415) 327-4800.

May 7-9—**Advances in Pediatrics.** UCSF. Thursday-Saturday. Review of major reappraisals in some aspects of the specialty, clinical implications of advances in cytology, physiology, immunology and endocrinology.

May 18-19—**Hearing in Children.** UCLA. Monday-Tuesday.



May 21-22—**Pediatric Otolaryngology—Medical Otolaryngology Problems.** UCLA. Thursday-Friday.

### Grand Rounds—Pediatrics

#### Tuesdays

8:00 a.m., Childrens Hospital Medical Center, Oakland.

8:30 a.m., Auditorium, Childrens Division Building, Los Angeles County-USC Medical Center, Los Angeles. USC.

8:30 a.m., Room 4-A, Kern County General Hospital, Bakersfield. CRMP Area IV.

8:30 a.m., Pathology Auditorium, San Francisco General Hospital.

#### Wednesdays

8-9:00 a.m., held alternately at Auditorium, Orange County Medical Center and Auditorium, Childrens Hospital of Orange County. UCI.

8:30 a.m., Bothin Auditorium, Childrens Hospital, San Francisco.

#### Thursdays

8:30-10:00 a.m., Room 664, Science Building, UCSF.

8:30-9:30 a.m., Lebanon Hall, Cedars of Lebanon Hospital, Los Angeles.

8:30 a.m., First Floor Auditorium, Harbor General Hospital, Torrance.

#### Fridays

8:00 a.m., Lecture Room, A Floor, Health Sciences Center, UCLA. CRMP Area IV.

8:30 a.m., Stanford University Medical Center, Palo Alto.

8-9:00 a.m., Lecture Hall, Childrens Hospital of Los Angeles.

Infectious Disease Grand Rounds. 10:00 a.m., Auditorium, Childrens Division Building, Los Angeles County-USC Medical Center, Los Angeles. USC.

## PSYCHIATRY

March 20-21 — **Suicide Prevention—Advanced Workshop.** UCSF. Friday-Saturday. Staffing, program evaluation and funding of suicide centers; research in suicide prevention; follow-up systems and methods; data collection.

March 21—**Psychiatric Perspectives in Medicine—An Introduction to Family Evaluation and Family Intervention.** UCSF at Stockton State Hospital, Stockton. Saturday. Principles of family organization, methods of family assessment, demonstration of family interview. 4½ hrs. \$7.50.

March 23-26—**The Urban Scene.** American Orthopsychiatric Association. See Community Medicine, March 23-26.

April 4-5—**The Brain and Its Behavior.** UCSF at Agnews State Hospital, San Jose. Saturday-Sunday. New developments in chemistry, neuroanatomy, and neurophysiology related to human behavior. \$15. 11 hrs.

April 4-5—**The Psychiatrist Consultant in Therapeutic Abortion.** USC Division of Postgraduate Psychiatry at Sheraton Universal Hotel, North Hollywood. Saturday-Sunday. For psychiatrists only. \$35. 10 hrs. Contact: Donald F. Naftulin, M.D., Director, Division of

Postgraduate Psychiatry, USC. (213) 225-1511, ext. 336.

April 8-June 10—**Group Methods.** UCSF at V.A. Hospital, San Francisco. Wednesdays 11:30-1:00. Weekly lectures and participants assigned to clinic groups. \$25. 15 hrs.

April 11-12—**The Suicidal Patient: New Approaches to Recognition and Treatment.** UCLA. Saturday-Sunday. Presentation of some of the special treatment diagrams now used at UCLA Neuropsychiatric Institute. \$60. 11½ hrs.

April 18 & 25—**Critical Issues in Mental Health.** University of California Extension, Riverside, at Cafeteria, University Commons, UC Riverside. Two Saturdays. 14 hrs. Contact: Ray Olitt, Health Services Coordinator, UC Extension, Riverside 92502. (714) 787-4329.

May 2—**Use of Imagination in Psychotherapy.** UCSF. Saturday. Dreams and Fantasies in Psychoanalytically Oriented Psychotherapy, Images in Jungian Therapy, Image Formation Techniques in Gestalt Therapy, Systematic Desensitization—A Form of Behavior Therapy, Impulsive Therapy, Uses of Image Formation in Other Schools of Therapy. 5½ hrs.

May 2-3—**Further Explorations in Group Therapy.** UCSF at Modesto State Hospital, Modesto. Saturday-Sunday.

May 7-11 — **American Psychoanalytic Association.** Sheraton Palace Hotel, San Francisco. Thursday-Monday. \$15 for non-members. Contact: Mrs. Helen Fischer, Exec. Sec., APA, 1 East 57th Street, New York 10022. (212) 265-0430.

May 8-10—**American Academy of Psychoanalysis—Annual Meeting.** Jack Tar Hotel, San Francisco. Friday-Sunday. Contact: Mollie Carroll, 125 East 65th Street, New York 10021. (212) 879-8950.

May 8-10—**Society for Biological Psychiatry.** Hilton Hotel, San Francisco. Friday-Sunday. Personality Disorders. 24 hrs. Contact: George N. Thompson, M.D., Sec.-Treas., SBP, 2010 Wilshire Blvd., Los Angeles 90017. (213) 483-7863.

May 9-10—**Psychiatry and the Law.** UCSF at Humboldt State College, Arcata. Saturday-Sunday.

May 10—**Association for the Advancement of Psychotherapy.** Civic Auditorium, San Francisco. Sunday. Contact: Stanley Lesse, M.D., Pres., AAP, 15 W. 81st Street, New York 10024. (212) 873-9233.

May 11-15—**American Psychiatric Association.** Civic Auditorium and Brooks Hall, San Francisco. Monday-Friday. Contact: Robert S. Garber, M.D., Exec. Sec., Carrier Clinic, Belle Mead, New Jersey 08502. (201) 359-3101.

May 14-16—**Mental Health — 2½ Day Symposium.** UCSF. Thursday-Saturday.

May 16-17—**Progress in Psychotherapy.** UCSF at Napa State Hospital, Imola. Saturday-Sunday.

May 23-24—**Residential Care for the Mentally Ill Patient.** UCSF at DeWitt Hospital, Auburn. Saturday-Sunday.

## RADIOLOGY—PATHOLOGY

April 1-5—**Clinical Cytology for Pathologists.** UCSF at St. Francis Hotel, San Francisco. Wednesday-Sunday.



Cytopathology of urinary tract, female genital tract following irradiation, non-neoplastic lesions of the lung. \$75. 10½ hrs.

**April 17-30—Radiology of the Gastrointestinal Tract.** USC, Princess Carla Cruise to Mexico from Los Angeles. Two weeks. \$200. 28 hrs.

**May 9—Diseases of the Gastrointestinal Tract.** South Bay Radiology Society and South Bay Pathology Society at Carmel Theater, Carmel. Saturday 1:30-5:30. Separate morning workshop in tube biopsy processing technique and interpretation. 4 hrs. Contact: Robert Rinehart, M.D., Dept. of Pathology, Santa Clara Valley Medical Center, 751 South Bascom Ave., San Jose 95128. (408) 293-0262, ext. 491.

**May 16—Radiology Society of Southern California.** Hotel del Coronado, Coronado. Saturday. Contact: Gladden V. Elliott, M. D., 5565 Grossmont Center Drive, Suite 1, La Mesa 92041.

**Continuously—Principles and Clinical Uses of Radioisotopes.** UCSF. Fundamentals for the proper understanding and use of radioactivity in clinical medicine. Training in diagnostic and therapeutic uses of radioisotopes. Normal period of training: 3 months. Two part course: Part A, Basic Fundamentals; Part B, Clinical Applications.

**Continuously—Mammography.** UCSF Mammography Section, Department of Radiology. Three days weekly, beginning with Tuesday. Call several days in advance. Contact: Richard H. Gold, M.D., Mammography Section, Department of Radiology, UCSF. (415) 666-1918.

#### **Grand Rounds—Radiology**

##### **Fridays**

Neuroradiology Grand Rounds. 9:30 a.m., held alternately at Stanford University Hospital and Neurology Conference Building 7, V.A. Hospital, Palo Alto, STAN.

#### **SURGERY—ANESTHESIOLOGY**

**March 25-28—Neurosurgical Society of America.** Ojai Valley Inn, Ojai, Calif. Wednesday-Saturday. Contact: William F. Collins, M.D., Secretary, NSA, 789 Howard Avenue, New Haven, Conn. 06510. (203) 436-1212.

**April 8-9—Medical Surgical Gastroenterology.** See Medicine, April 8-9.

**April 9-10—General Surgery.** UCSF at St. Francis Hotel, San Francisco. Thursday-Friday. Emergency room problems, current concepts of surgery for bleeding varices, chronic pancreatitis, cholecystitis, ulcerative colitis, diverticulitis, intestinal fistula, abdominal trauma. Recent observations in advanced breast cancer, malignant disease, calcium metabolism, gastric physiology. \$65. 11½ hrs.

**April 11-12—Los Angeles County Society of Anesthesiologists—15th Annual Postgraduate Assembly.** Los Angeles Hilton Hotel. Saturday-Sunday. 15 hrs. Contact: Leo A. Parker, M.D., 8422 Jamieson St., Northridge 91324. (213) 345-6763.

**June 4-6—Highlights of Ophthalmology.** PMC Department of Ophthalmology at PMC. Thursday-Saturday. Cryosurgery, Fluorescein angiography, glaucoma, cataract surgery, diabetic retinopathy, retinal detachment,

adhesives in surgery, contact lenses and ultrasonography. \$125. Contact: Wayne L. Erdbrink, M.D., Director of Residency Training, Dept. of Ophthalmology, PMC.

**June 4-6—Rheumatoid Arthritic Surgery.** UCSF and American Academy of Orthopaedic Surgeons at UCSF. Thursday-Saturday. Contact: UCSF.

**June 12-14—California Society of Anesthesiologists—4th Biennial Scientific Meeting.** Sahara-Tahoe Hotel, South Shore, Lake Tahoe. Friday-Sunday. The Anesthesiologist and His Relationship to Other Specialties. 8 hrs. Contact: Norman R. Catron, Exec. Sec., CSA, 100 So. Ellsworth Ave., Suite 401, San Mateo 94401. (415) 343-4644.

#### **Grand Rounds—Surgery**

##### **Wednesdays**

7:15 a.m., Auditorium, Kern County General Hospital, Bakersfield. CRMP Area IV.

1st and 3rd Wednesdays. 11:00 a.m., Auditorium, Brown Building, Mount Sinai Hospital, Los Angeles. CRMP Area IV.

##### **Thursdays**

Neurology and Neurosurgery Grand Rounds. 11:00-12:15. Room 663, Science Building, UCSF.

##### **Fridays**

1-2:00 p.m., Auditorium, Orange County Medical Center, Orange. UCI.

Neurosurgery. 11:15 a.m., held alternately at Stanford University Hospital and Neurology Conference Building 7, V.A. Hospital, Palo Alto, STAN.

##### **Saturdays**

8:00 a.m., Auditorium, 1st floor, University Hospital of San Diego County, San Diego. UCSD.

9:00 a.m., Room 73-105, Health Sciences Center, UCLA. CRMP Area IV.

8:30 a.m., Assembly Room, Harbor General Hospital, Torrance. CRMP Area IV.

#### **OF INTEREST TO ALL PHYSICIANS**

**March 18—Annual Medical Staff Symposium—Memorial Hospital of Long Beach.** Memorial Hospital of Long Beach. Wednesday. Contact: Norman R. Nager, Director of Public Relations, Memorial Hospital of Long Beach, 2801 Atlantic Avenue, Long Beach 90801. (213) 595-2311.

**March 18—Advances in Clinical Genetics.** USC. Wednesday. Application of genetics information to problems in clinical medicine. Methods of diagnosis and changes in patient management due to advances in clinical genetics. \$25. 6 hrs.

**March 19-20—Postgraduate Seminar and Clifford Sweet Memorial Lecture.** Childrens Hospital of Oakland. Thursday-Friday. Sex Education for Physicians. Contact: Inetta Carty, Childrens Hospital of Oakland, 51st and Grove Streets, Oakland 94609. (415) 654-5600.

**March 25-26—Los Angeles County Heart Association and Los Angeles Academy of General Practice—Seventh Annual Spring Symposium for Physicians Practicing General Medicine.** Wednesday-Thursday.

### **CMA Postgraduate Institutes and Circuit Courses**

**April 2-3—West Coast Counties Regional Postgraduate Institute.** CMA, UCD and Monterey County Medical Society at Del Monte Hyatt House, Monterey. Thursday-Friday. Endocrine Problems with Children (including Diabetes), Infectious Diseases, Cardiac Disease and its Rehabilitation, the Physician and Family Problems. \$20. 12 hrs. Contact: CMA.

**May 8-9—San Joaquin Valley Counties Regional Postgraduate Institute.** CMA, USC, and Fresno County Medical Society at Ahwahnee Hotel, Yosemite. Friday-Saturday. Concurrent symposia in Adolescent Medicine, Coronary Care, Sensitivity Training, and Problems in the Practice of Medicine. \$20. 10 hrs. Contact: CMA.

**May 15-16 — Redwood Regional Conference.** CMA, UCSF at Konocti Harbor Inn, Clear Lake. Friday-Saturday. The Anemias and Musculo/Skeletal Conditions in Daily Practice. \$20. Contact: CMA.

Contact: Joe Kennelly, Director, Public Information, LACHA, 2405 W. Eighth Street, Los Angeles 90057. (213) 385-4231.

**April 17-18—Infectious Diseases.** UCSF. See Pediatrics, April 17-18.

**April 19—Office Emergencies: A Symposium for Medical Assistants.** UCSF. Sunday. \$12.50. 6 hrs.

**April 23-25—First Annual Hospital Medical Staff Conference—Medical Staff Leadership: Fact or Fiction.** USC at Monte Corona Conference Center, Twin Peaks. Thursday-Saturday. \$100. 18 hrs.

**April 23-May 21—Environmental Pollution.** UCLA. Thursdays.

**April 25-26—Sex in Modern Society.** UCSF at Flamingo Motor Hotel, Santa Rosa. Saturday-Sunday. \$15. 8 hrs.

**May 1-2—Trauma.** UCSF at Mary's Help Hospital, Daly City. Friday-Saturday.

**May 3-9—Hawaii Medical Association.** Hawaiian Village, Honolulu. Sunday-Saturday. Contact: Miss Lee McCaslin, Exec. Sec., HMA, 510 Beretania Street, Honolulu 96813. (808) 536-7702.

**May 6—Annual Seminar—N.E. Sub-Chapter, Los Angeles County Academy of General Practice.** Santa Teresita Hospital, Duarte. Wednesday. \$15. 3 hrs. Contact: John A. Corbin, M.D., 924 Buena Vista Avenue, Duarte 91010 (213) 358-455.

**May 8-9—Population Explosion, Birth Control, Sexual Revolution.** University of California Extension,

Riverside, at Watkins Hall, UC Riverside. Friday-Saturday. 10 hrs. Contact: Ray Olitt, Health Services Program Coordinator, UC Extension, Riverside 92502. (714) 787-4329.

**May 20—Medical Practices in Central America and Mexico.** Agnews State Hospital at Agnews State Hospital, San Jose. Wednesday. 1½ hrs. Contact: J. Elizabeth Jeffress, M.D., Agnews State Hospital, San Jose 95114. (408) 262-2100.

**May 22-23—Conference on Pregnant Teenagers.** USC at International Hotel, Los Angeles. Friday-Saturday. 12 hrs.

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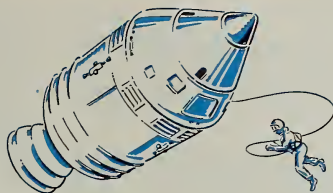
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**ALLERGY IN CHILDREN—**Louis Tuft, M.D., Formerly Chief of the Allergy Clinic and Clinical Professor of Medicine (Emeritus), Temple University Medical Center, Philadelphia; and Harry Louis Mueller, M.D., Chief, Division of Allergy, The Children's Hospital Medical School, Boston; Lecturer in Pediatrics, Harvard Medical School, Boston. W. B. Saunders Company, West Washington Square, Philadelphia, Pa. (19105), 1970. 561 pages, \$19.50.

**AUTOGENIC THERAPY—VOLUME III—APPLICATIONS IN PSYCHOTHERAPY—**Wolfgang Luehe, M.D., Dr. med. (Hamburg), L.M.C.C. (Ottawa), Scientific Director, Oskar Vogt Institute, Kyushu University, Fukuoka; (visiting) Professor of Psychophysiology Therapy, Medical Faculty, Kyushu University, Japan. Formerly Assistant Professor of Psychophysiology, University of Montreal; and Johannes H. Schultz, M.D., Dr. med. (Göttingen), Dr. h.c. (Tübingen), Professor of Neuro-Psychiatry, Berlin, West Germany. Grune & Stratton, Inc., 381 Park Avenue South, New York, N.Y. (10016), 1969. 228 pages, \$11.75.

**CARDIOVASCULAR SURGERY—CURRENT PRACTICE—**Volume I—Thomas H. Burford, M.D., Professor of Clinical Thoracic and Cardiovascular Surgery, Washington University School of Medicine; Associate Thoracic Surgeon, Barnes Hospital and St. Louis Children's Hospital, St. Louis, Missouri; and Thomas B. Ferguson, M.D., Associate Professor of Clinical Thoracic and Cardiovascular Surgery, Washington University School of Medicine; Attending Thoracic Surgeon, Barnes Hospital and St. Louis Children's Hospital, St. Louis, Missouri. The C. V. Mosby Company, 3207 Washington Blvd., St. Louis, Mo. (63103), 1969. 273 pages, \$18.00.

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**DRUGS OF CHOICE—1970-1971—**Edited by Walter Modell, M.D., Professor of Pharmacology, Cornell University Medical College, New York; Member, Executive Committee, United States Pharmacopeia; Editor, Clinical Pharmacology and Therapeutics; Editor, Pharmacology for Physician. The C. V. Mosby Company, 3207 Washington Blvd., St. Louis (63103), 1970. 924 pages, \$20.50.

**ENERGETICS: YOUR KEY TO WEIGHT CONTROL —**Grant Gwinup, M.D. Sherbourne Press, Inc., 1640 South La Cienega Blvd., Los Angeles, Ca. (90035), 1970. 176 pages, \$4.95.

**THE EXECUTIVE DIET—How to Eat in Fine Restaurants and Still Maintain Your Proper Weight—**Austin H. Schoen, M.D., and William I. Kaufman. Corinthian Editions, Inc., 500 Fifth Avenue, New York, N.Y. (10036), 1969. 116 pages, \$1.95. (Paperback)

**VITAMIN E FOR AILING AND HEALTHY HEARTS—**Wilfrid E. Shute, M.D., with Harald J. Taub. Pyramid House, Pyramid Publications, 444 Madison Avenue, New York, N.Y. (10022), 1969. 206 pages, \$6.95.

**FRONTIERS OF PULMONARY RADIOLOGY—**Pathophysiologic, Roentgenographic and Radioisotopic Considerations—Proceedings of the Symposium sponsored by Harvard Medical School, April 21-22, 1967—Edited by Morris Simon, M.D., Associate Clinical Professor of Radiology, Harvard Medical School; Radiologist-in-Chief, Beth Israel Hospital, Boston; E. James Potchen, M.D., Associate Professor of Radiology, Director, Nuclear Medicine, Edward Mallinckrodt, Institute of Radiology, Washington University, St. Louis, Missouri; and Marjorie Le May, M.D., Assistant Clinical Professor of Radiology, Harvard Medical School; Radiologist to Harvard University Health Service, Cambridge. Grune & Stratton, Inc., 381 Park Avenue South, New York, N.Y. (10016), 1969. 424 pages, \$34.50.

**A GUIDE TO DERMATOHISTOPATHOLOGY—**Hermann Pinkus, M.D., Professor and Chairman, Department of Dermatology and Syphilology, Associate, Department of Pathology, Wayne State University School of Medicine, Detroit, Michigan; Senior Attending Dermatologist, Detroit General Hospital; Chief, Dermatology Section, Veterans Administration Hospital, Allen Park, Michigan; and Amir H. Mehregan, M.D., Adjunct Associate Professor, Department of Dermatology and Syphilology, Associate, Department of Pathology, Wayne State University School of Medicine, Detroit, Michigan; Senior Associate Dermatologist, Detroit General Hospital. Appleton-Century-Crofts, Division of Meredith Publishing Company, 440 Park Avenue South, New York, N.Y. (10016), 1969. 546 pages, \$20.00.

**HANDBOOK OF PSYCHIATRY—**Edited by Philip Solomon, M.D., Formerly Clinical Professor of Psychiatry, Harvard Medical School, and Physician-Chief, Psychiatry Service, Boston City Hospital, and Vernon D. Patch, M.D., Assistant Professor of Psychiatry, Harvard Medical School, and Acting Director, Psychiatry Service, Boston City Hospital. Lange Medical Publications, Drawer L, Los Altos, Ca. (94022), 1969. 623 pages.

**INFECTIOUS AGENTS AND HOST REACTIONS —**Edited by Stuart Mudd, M.A., M.D., Professor Emeritus of Microbiology, The University of Pennsylvania School of Medicine; Past President, The International Association of Microbiological Societies; Chief, Microbiologic Research Program, Veterans Administration Hospital, Philadelphia. W. B. Saunders Company, Publisher, West Washington Square, Philadelphia, (19105), 1970. 626 pages, \$22.50.

**JUVENILE RHEUMATOID ARTHRITIS—**Major Problems in Clinical Pediatrics—Earl J. Brewer, Jr., M.D., Assistant Professor, Department of Pediatrics, Baylor College of Medicine, Chief, Arthritis Clinical Research Center, Texas Children's Hospital, Houston. W. B. Saunders Company, Publisher, West Washington Square, Philadelphia (19105), 1970. 231 pages, \$11.50.

**LASER PHOTOCOAGULATION AND RETINAL ANGIOGRAPHY —**With Current Concepts in Retinal and Choroidal Diseases—H. Christian Zweng, M.D., Staff Ophthalmologist, Palo Alto Medical Clinic, Palo Alto, California; Associate Clinical Professor, Surgery (Ophthalmology), Stanford University School of Medicine, Stanford; Senior Research Associate, Stanford Research Institute, Menlo Park; Senior Research Associate, Palo Alto Medical Research Foundation, Palo Alto; Hunter L. Little, M.D., Staff Ophthalmologist, Palo Alto Medical Clinic, Palo Alto; Assistant Clinical Professor, Surgery (Ophthalmology), Stanford University School of Medicine, Stanford; Research Associate, Stanford Research Institute, Menlo Park; and Robert R. Peabody, M.D., Clinical Instructor, Surgery (Ophthalmology), Stanford University School of Medicine, Stanford; Research Associate, Stanford Research Institute, Menlo Park; Consultant in Ophthalmology, Veterans Administration Hospital, Palo Alto; Consultant in Ophthalmology, Sacramento Medical Center, Sacramento. The C. V. Mosby Company, 3207 Washington Blvd., St. Louis, Mo. (63103), 1969. 297 pages, \$26.50.

**MENTAL RETARDATION—An Annual Review—**Edited by Joseph Wortis, M.D., Director of Developmental Services and Studies, Department of Psychiatry, Maimonides Medical Center, Brooklyn, N.Y. Grune & Stratton, Inc., Publishers, 381 Park Avenue South, New York (10016), 1970. 321 pages, \$19.75.

**PROGRESS IN LIVER DISEASES—Volume III—**Edited by Hans Popper, M.D., Ph.D., Professor and Chairman of the Department of Pathology, Mount Sinai School of Medicine of the City University of New York; and Fenton Schaffner, M.D., M.S., Professor of Pathology and Medicine, Mount Sinai School of Medicine of the City University of New York; and with 51 contributors. Grune & Stratton, Inc., 381 Park Avenue South, New York, (10016), 1970. 562 pages, \$25.75.

**PROGRESS IN NEUROLOGY AND PSYCHIATRY—AN ANNUAL REVIEW—Volume XXIV—**Edited by E. A. Spiegel, M.D., Dr. med. (Hon.), Emer. Professor and Head of the Department of Experimental Neurology, Temple University School of Medicine, Philadelphia. Grune & Stratton, Inc., 381 Park Avenue South, New York, N.Y. (10016), 1969. 541 pages, \$24.75.

**THE RIGHT TO ABORTION: A PSYCHIATRIC VIEW—**Formulated by the Committee on Psychiatry and Law of the Group for the Advancement of Psychiatry, Report Number 75 (Volume VII, October 1969), 25 pages. Copies may be obtained at \$1.00 each from the Publications Department, Group for the Advancement of Psychiatry, 310 Park Avenue South, New York, N.Y. (10016). Quantity prices are available upon request.

**TEXTBOOK OF NUCLEAR MEDICINE TECHNOLOGY—**Paul J. Early, B.S., Physicist, Nuclear Medicine Institute, Cleveland, Ohio; Muhammad Abdel Razak, M.B.B.Ch., D.M., M.D., Assistant Professor, Medical Unit, and Division of Nuclear Medicine, Faculty of Medicine, Cairo University, Cairo, U.A.R.; and D. Bruce Sodex, M.D., F.A.C.P., Associate Professor of Radiology (Nuclear Medicine), George Washington University, Washington, D.C.; Director, Nuclear Medicine Institute, Cleveland, Ohio. The C. V. Mosby Company, 3207 Washington Boulevard, St. Louis, Mo. (63103), 1969. 378 pages, with 241 illustrations, \$15.50.



# Diabetic Ketoacidosis

## A Review of Cases at a University Medical Center

JOHN F. KIRALY, M.D., CHARLES E. BECKER, M.D., AND  
HIBBARD E. WILLIAMS, M.D., *San Francisco*

■ *Twenty-five cases of diabetic ketoacidosis were studied retrospectively with respect to clinical characteristics and results of therapy. In this series (as with all 88 patients admitted in the last five years with a diagnosis of diabetic ketoacidosis) there were no deaths. Infection was found to be the most common precipitating event, documented by physical findings and cultures in one-third of these cases.*

*In about two-thirds of the cases, electrocardiograms which were read as abnormal on admission reverted to normal after therapy.*

*In all patients serum potassium levels decreased from admission values; one patient became symptomatically hypokalemic.*

*Low serum potassium levels on admission and early vigorous bicarbonate therapy are emphasized as major predisposing factors of symptomatic hypokalemia. None of the patients had overt hyperosmolar coma, lactic acidosis or cerebral edema during therapy.*

DIABETIC KETOACIDOSIS remains one of the most severe, life-threatening complications in diabetic patients, despite early diagnosis, apparently adequate therapy and increased awareness by both patient and physician. Although the advent of insulin decidedly lowered the fatality rate in this disorder, the mortality has been noted to vary be-

tween 1.5<sup>1</sup> and 31.4 percent<sup>2</sup> during the past 20 years. In 1962 a mortality of 5 percent among 401 patients was reported from the Joslin Clinic and in that series 12 percent of patients over the age of 60 died as a result of this complication of diabetes.<sup>3</sup>

Many factors have been implicated in the lowering of mortality in this disorder, including earlier recognition, awareness of the high incidence of infection as a precipitating factor, better understanding of the metabolic aberrations and electrolyte disturbances, and more rational use of insulin,

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intravenous fluids and potassium replacement. Despite these advances in knowledge in most large hospitals, diabetic ketoacidosis remains a serious and often lethal disorder requiring concentrated and continuous therapeutic efforts by a team of medical personnel.

During the past five years at the University of California Medical Center, San Francisco, no patient has died as a result of diabetic ketoacidosis. An analysis of the records of 25 patients with ketoacidosis admitted to this hospital during this period forms the basis of this report. Emphasis will be placed on the type of patient, precipitating factors, clinical and laboratory characteristics and results of therapy.

## Clinical Material

Clinical material was gathered from hospital records coded for diabetic ketoacidosis between January 1964 and December 1968. A diagnosis of ketoacidosis was considered to be established if the following criteria were met:

- Initial serum carbon dioxide level was less than 15 mEq per liter.
- Acetone was present in blood and urine.
- Initial blood sugar was greater than 250 mg per 100 ml.\*

Using these criteria, 25 episodes of ketoacidosis in 19 patients were reviewed. Sixty-nine patients with diabetic ketoacidosis recorded during this period were eliminated from this review because of failure to meet the three criteria noted above. Although these patients are not included in this summary, it is important to note that none of them died.

Laboratory studies reported in this review were performed in the Clinical Laboratories of the University of California Medical Center. Serum acetone determinations were estimated by the medical housestaff using Acetest® tablets.<sup>4</sup> Electrocardiographic interpretations were made by the Cardiology Service of the Medical Center.

## Results

### *Clinical Background of the Patients*

**Age and Sex:** The average age of the 19 different patients studied in this series at the time of their first admission to the Medical Center in dia-

betic acidosis was 32.6 years and the range was from 13 to 57 years. In the 17 patients with known diabetes before their first admission to the Medical Center the average duration of the disease before their first admission was 12.3 years and the average age of onset was 24 years. Only three patients had onset of diabetes after age 35 and none in this series had the onset of the disease after the age of 40 years. Fourteen of the 19 patients were female and five were male.

**Diabetic History:** A family history of diabetes was elicited from eight of the patients. Nine patients gave a history of episodes of diabetic ketoacidosis before their first admission to the Medical Center, more than one such episode in all cases.

At the time of the first admission to the Medical Center in ketoacidosis, all of the 17 patients with known diabetes were being managed with some form of insulin, either alone or in combination with an oral agent (phenformin). None of the patients in this series was being treated with oral hypoglycemic agents alone. In 23 of the 25 admissions of the patients with previously known diabetes, the patients had been previously stabilized on a relatively fixed daily insulin dosage, requiring an average of 44 units per day (ranging from 6 to 100 units per day).

In only six of the 19 patients studied was a history of previous insulin reaction obtained. The frequency of reactions was quite variable, ranging from only a single episode to multiple episodes yearly.

### *Clinical Data*

**Precipitating Factors:** The most common precipitating factor of diabetic acidosis in the 25 episodes studied was infection (Table 1). In eight cases infection was documented by either physical findings or appropriate cultures: the documented infections included four cases of acute pharyngitis, two cases of pneumonia, two cases of otitis media, and one case of necrotizing, ulcerating, gingivitis from which *Borrelia vincenti* was cultured. In six cases a history consistent with an antecedent infection was obtained. In four of the six the history was consistent with an influenza-like syndrome characterized by fever, chills, malaise, cough, coryza, and myalgias; the remaining two patients appeared to have had acute gastroenteritis. Thus, in 14 of the 25 cases infection presumably was the precipitating factor.

\*One patient had blood sugar of 84 mg per 100 ml at the time of hospital admission but had administered large doses of insulin to herself before admission.



TABLE 1.—*Precipitating Factors in 25 Cases of Diabetic Ketoacidosis*

	<i>Number of Cases</i>	<i>Percent</i>
Documented Infection . . . . .	8	32
a. Vincent's Angina . . . . .	1	
b. Streptococcal Pharyngitis . . . . .	2	
c. Pneumonia* . . . . .	2	
d. Otitis Media* . . . . .	2	
e. Sterile exudative pharyngitis . . . . .	2	
History of Antecedent Infection . . . . .	6	24
a. "Flu" Syndrome . . . . .	4	
b. Gastroenteritis . . . . .	2	
Miscellaneous Factors . . . . .	8	32
a. Omission of insulin . . . . .	3	
b. Alcoholic excess . . . . .	2	
c. Congestive heart failure . . . . .	1	
d. Sunburn . . . . .	1	
e. Roto-scoliosis . . . . .	1	
Unknown . . . . .	3	12
Total . . . . .	25	100

\*One patient presented with concurrent otitis media and pneumonia.

The second most common precipitating factor was omission of insulin — three cases. In three cases no precipitating factor was evident; and the five remaining cases were precipitated apparently by alcoholic excess (two cases), congestive heart failure (one case), sunburn (one case), and roto-scoliosis (one case).

One of the two cases of diabetic acidosis in patients with newly diagnosed diabetes was clearly precipitated by streptococcal pharyngitis. In the other no precipitating factor could be found but the patient had a history of polydipsia, polyuria, nocturia, polyphagia and weight loss over a period of seven weeks.

In light of these precipitating factors, the effect of attempting to abort an incipient episode of diabetic acidosis on the course of the illness was studied. In nine admissions a history of an attempt to abort the incipient episode of acidosis was obtained; however, two patients reported they stopped taking insulin to abort the episode, while the other seven responded by increasing their insulin dosage. No correlation could be established between the severity of the ketoacidosis and attempts by the patient to abort the episode.

**Symptoms:** Each of the 25 cases in this study was surveyed for the presence of seven symptoms of diabetic ketoacidosis (Table 2). The most commonly elicited symptom was nausea and vomiting, present in 22 cases. The second most common was polyuria (11 cases), while polydipsia (nine cases) ranked third in prevalence. Of the remaining four symptoms, abdominal pain was reported in

TABLE 2.—*Incidence of Symptoms of Diabetic Ketoacidosis in 25 Cases*

	<i>Number of Cases</i>
Nausea and vomiting . . . . .	22
Polyuria . . . . .	11
Polydipsia . . . . .	9
Abdominal pain . . . . .	4
Polyphagia . . . . .	2
Myalgias . . . . .	1
Pleural pain . . . . .	1

TABLE 3.—*Physical Findings in 25 Cases of Diabetic Ketoacidosis*

	<i>Number of Cases</i>
Dehydration . . . . .	22
Kussmaul respiration . . . . .	14
Hyporeflexia . . . . .	16
Hyperreflexia . . . . .	2
Altered state of consciousness . . . . .	15
Stuporous-semi-comatose . . . . .	13
Comatose . . . . .	2
Hepatomegaly . . . . .	4
Abdominal tenderness or rigidity . . . . .	0
<i>Vital Signs</i>	<i>Mean</i> <i>Range</i>
Temperature (degrees centigrade) . . . . .	36.9      (35.9-37.9)
Pulse (beats per minute) . . . . .	115      (80-165)
Respiration (breaths per minute) . . . . .	30      (14-44)
Systolic Blood Pressure (mm. of Hg.) . . . . .	122      (90-172)

four cases, polyphagia in two, myalgias in one, and pleuritic chest pain in one. Polydipsia, polyuria, polyphagia and abdominal pain were always noted as being absent in the records, while the absence of nausea and vomiting, myalgias, and pleural pain was never listed.

**Physical Findings:** Most prevalent of the physical findings of diabetic ketoacidosis in the 25 cases reviewed were signs of dehydration, present in 22 cases (Table 3). Of the various signs of dehydration, dryness of the skin, tongue, and mucous membranes were reported in all of these 22 patients; diminished turgor of the skin was reported in five, and softness of the eyeballs in four.

In all patients the status of the deep tendon reflexes was recorded in a semiquantitative fashion. Generally they were recorded as normal, hyporeflexic or hyperreflexic or were graded on a scale of 0 to 4+. For this study, reflexes on the 0 to 4 scale were reclassified as normal if either 2+ or 3+, and as hyperreflexic if 4+ or hyporeflexic if 1+ to 0. Thus 16 patients were classified as hyporeflexic, the second most common sign of diabetic acidosis.

To study the state of consciousness, a classification of three categories was established, which characterized the state of consciousness as (1) alert, (2) stuporous to semi-comatose, and (3) comatose. Among the 25 patients whose cases were studied 15 had an altered state of consciousness, 13 being considered stuporous or semi-comatose and two comatose; the remaining ten patients were judged to be alert.

Kussmaul respirations were recorded as a positive finding in 14 cases, but this frequent finding in diabetic ketoacidosis was not recorded among the pertinent negatives in any of the 13 remaining cases.<sup>5</sup>

Hepatomegaly was reported as a positive finding in four cases, and was not present in the remaining 21 cases. Hepatomegaly was slight in all four cases, varying between 2 and 4 centimeters of enlargement. Only one of the two patients with a history of alcoholic excess had liver enlargement. Hypoactive bowel sounds were reported in eight cases; in 14 cases the sounds were normal. In none of the patients was abdominal tenderness or rigidity elicited, although four complained of abdominal pain.

### Diabetic Complications

The records of all 19 patients were surveyed for evidence of the complications of diabetes at the time of the patient's first Medical Center admission in diabetic ketoacidosis.

**Retinopathy:** Eight patients had one or more of the classical stigmata of diabetic retinopathy, ranging from microaneurysms to advanced retinitis proliferans and blindness, on their first Medical Center admission.

**Neuropathy:** Five patients had polyneuropathy of stocking-glove type noted on their first admission in ketoacidosis, but in all cases the neurological examination was perfunctory on admission and was not repeated when the patient had recovered. None of the patients was reported to have had mononeuropathy, autonomic neuropathy or amyotrophy.

**Myocardial Disease:** Three patients could be classified as having myocardial disease on their first admission for ketoacidosis. One patient was admitted in congestive heart failure, one was being treated with nitroglycerin for pre-infarction angina, and one had evidence of an old anterior-septal infarction on serial electrocardiograms.

**Peripheral Vascular Disease:** Four patients were found to have evidence of peripheral vascular disease on their first admission for ketoacidosis. One had evidence of small vessel disease, showing delayed blushing of the hands and feet. Two had signs of arterial vascular disease — absence of popliteal and dorsalis pedis pulses bilaterally in one case, and objective intermittent claudication in the other. The fourth patient had signs of venous disease in both legs, with stasis dermatitis of both extremities.

**Renal Disease:** Two patients in this series had a documented history of recurrent episodes of pyelonephritis. None of them had a history of chronic renal disease (all had normal serum creatinine levels when not in ketoacidosis).

**Vital Signs:** In all cases the vital signs were recorded on admission (Table 3). Oral temperatures were recorded in all cases except three in which temperature was taken rectally because the patients were in coma or semi-coma. The average temperature for all 25 cases on admission was 36.9°C, with a range of 35.9 to 37.9 C.

Tachycardia (pulse rate greater than 100 beats per minute) was present in 23 cases; the average was 115 beats per minute and the range 80 to 165.

Tachypnea (respiratory rate over 24 per minute) was present in 18 cases. The average was 30 inspirations per minute and the range was 14 to 44.

Systolic blood pressure on admission ranged between 90 and 172 mm of mercury with an average pressure of 122 mm. None of the patients was admitted in clinical shock; in only one case was a systolic blood pressure less than 100 mm recorded.

### Initial Laboratory Values

**Blood Sugar:** The blood sugar level was determined in all cases at the time of admission to hospital (Table 4). The average blood sugar level was 533 mg per 100 ml, with a range of 84 to 1,335 mg. The one patient with blood sugar of 84 mg per 100 ml had given herself large doses of insulin before admission. Acidosis was confirmed in this patient by the low serum carbon dioxide level and the presence of acetone in the serum and urine. Except for this patient, all patients admitted had blood sugar of more than 250 mg per 100 ml.

**Carbon Dioxide Combining Power:** All patients in this series were selected for having a carbon dioxide level less than 15.0 mEq per liter. The mean for the 25 patients on admission was 8.7 mEq and the range was from 2.6 to 14.9 mEq.

TABLE 4.—Laboratory Values in 25 Cases of Diabetic Ketoacidosis

Laboratory Test	Number of Cases	Mean	Range	Unit
Blood Sugar	25	533	(84-1335)	mg./100 ml.
Carbon Dioxide	25	8.7	(2.6-14.9)	mEq./L.
Serum Potassium	24	5.1	(3.3-8.0)	mEq./L.
Serum Sodium	23	134	(120-146)	mEq./L.
Serum Chloride	20	98.5	(84-106)	mEq./L.
Packed Cell Volume	25	46.5	(33-59)	Vol. %
White Blood Cell Count	25	20,000	(9800-47,000)	cells/cu. mm.
Serum Creatinine	15	3.1	(1.0-7.2)	mg./100 ml.
Serum Osmolality <sup>1</sup>	23	300	(273-323)	mOsm./L.
Anion Gap <sup>2</sup>	20	28.3	(19-40.9)	mEq./L.

<sup>1</sup>Calculated for this study using the following formula:  $2 \times \text{serum sodium} + \text{blood sugar}/20$ .

<sup>2</sup>Calculated for this study using the formula of Waters, et al<sup>6</sup>:  $(\text{serum sodium}) - (\text{serum chloride} + \text{CO}_2)$ .

**Serum Electrolytes:** In 24 of 25 of the cases in this series the mean serum potassium level determined at the time of admission to hospital was 5.1 mEq per liter and the range 3.3 to 8 mEq. Fifteen patients had serum potassium levels within the normal range of 3.5-5.3 mEq per liter, while eight had initial values exceeding the normal range, and only one had a value below the normal range. The serum sodium level, determined in 23 of the 25 cases, averaged 134 mEq per liter and varied between 120 and 146 mEq. The serum chloride level was determined in 20 cases. The mean was 98.5 mEq and the range was from 84 to 106 mEq per liter.

**White Blood Cell Count and Hematocrit:** The white blood cell count and hematocrit were determined in all cases at the time of hospital admission and in all cases the white cell counts demonstrated polymorphonuclear leukocytosis, with an average count of 20,000 cells per cu mm and a range from 9,800 to 47,000 per cu mm. In the eight cases in which infection was documented, polymorphonuclear leukocytosis was near the mean level. The average hematocrit was 46.5 percent with a range of 33 to 59 percent. Only two patients had hematocrits less than 40 percent on admission, and one of these was being treated for an iron deficiency anemia.

**Serum Creatinine:** The serum creatinine level, determined in 15 cases at the time of hospital admission, averaged 3.1 mg per 100 ml and the range was 1.0 to 7.2 mg per 100 ml. In all 25 cases, serum creatinine was determined sometime during the stay in hospital, and in all cases a normal creatinine level was found after adequate fluid and electrolyte therapy.

**Serum Osmolality:** The serum osmolality was calculated retrospectively in 23 cases in which sufficient data was available at the time of hospital

admission to make this calculation. The osmolality was estimated by doubling the serum sodium concentration and adding a factor of 1 milliosmole for every 20 mg per 100 ml of blood glucose. The mean calculated serum osmolality was 300 mOsmol per liter, with a range of 273 to 323 mOsmol per liter.

**Anion Gap:** The anion gap was calculated retrospectively in 20 cases in which sufficient data was available at the time of admission to make this determination. The anion gap was determined by subtracting the sum of the carbon dioxide level and the serum chloride concentration from the serum sodium concentrations.<sup>6</sup> The mean anion gap in these 20 cases was 28.3 mEq per liter and the range was 19 to 40.9 mEq per liter.

**Serum Acetone:** Serum acetone determinations with Acetest® tablets were performed at the time of admission in 24 cases. Five cases had positive acetone in a serum dilution of 1:8, ten cases were positive in a 1:4 dilution, seven cases were positive in a 1:2 dilution and in two cases there was a trace of acetone in undiluted serum.

**Urine Sugar and Acetone:** The urine sugar determination, as performed with Clinitest®, was reported as 4+ in all but three cases. In two of the exceptions the urine sugar was 3+ and in both of these cases "moderate" ketonuria was recorded. In the remaining case glycosuria was not demonstrated. The patient (previously mentioned as having injected a large amount of insulin not long before) had blood sugar of 84 mg per 100 ml and a large amount of serum and urine acetone.

Urine acetone determinations were performed with either Acetest® or Ketostix® and were recorded as being small, moderate or large, according to the supplier's brochure. Urinary acetone was recorded as "large" in 21 cases and as "moderate" in the remaining four cases.



TABLE 5.—*Electrocardiographic Findings in 22 Cases of Diabetic Ketoacidosis*

	<i>Number of Cases</i>
Normal . . . . .	7
Peaked T waves . . . . .	5
Depressed T waves with U waves . . . . .	2
Depressed T wave and S-T segments . . . . .	2
Nonspecific S-T segment abnormalities . . . . .	4
Ischemic pattern . . . . .	2

**Serum Amylase:** Serum amylase was determined in seven of the 25 patients and in only one case was an abnormal value reported: It was 820 Somogyi units (normal 70 to 150 units) but the patient had neither the history nor physical findings of acute pancreatitis.

**Blood Gases:** Arterial blood specimens were analyzed for pH and  $p\text{CO}_2$  level at the time of hospital admission in nine cases. The mean pH was 7.16 (range 7.09 to 7.25) and the mean  $p\text{CO}_2$  level was 21.3 mmols per liter.

**Electrocardiogram:** A tracing was made at the time of hospital admission in 22 cases (Table 5). In seven of them it was interpreted as showing a normal pattern, and in the remaining 15 some degree of abnormality was described. Thirteen patients had patterns consistent with an electrolyte abnormality, while two had tracings that were interpreted as more consistent with myocardial ischemia. In all but one case, the electrocardiogram reverted to normal after correction of the metabolic and electrolyte disturbances. In the one exception a pattern of myocardial ischemia was still present after correction of the metabolic and electrolyte abnormalities of diabetic ketoacidosis.

## Therapy

### Insulin

In the 24 cases in which the initial blood sugar level exceeded 250 mg per 100 ml, regular insulin was administered immediately after the completion of the initial laboratory tests in 16 cases and within one to six hours in the remaining eight cases. The average initial dose of regular insulin was 82 units and the range 20 to 200 units. The route by which the initial dose of insulin was given was intravenous in ten cases, subcutaneous in eight, intramuscular in one, split doses between intravenous and subcutaneous in four, and split between intravenous and intramuscular in one. The average dose of insulin given in the first 24 hours was 381 units (the range was 120 to 1,600 units), and in

the first 48 hours was 479 units (the range 160 to 1,725). At the time of discharge from the hospital the average daily insulin dose for the 23 patients with previously known diabetes had increased from a mean of 44 units daily at the time of hospital admission to a mean of 51 units per day at the time of discharge.

### Fluid and Electrolytes

In all cases intravenous fluid and electrolyte replacement therapy was begun as soon as urine and blood specimens for initial laboratory work had been obtained. In 13 cases normal saline was the first solution given after admission, and it was continued until the blood sugar level fell below 250 mg per 100 ml, at which time 5 percent dextrose in 0.5 normal saline solution was begun. In eight cases the first solution given was 5 percent dextrose in 0.5 normal saline solution; in these eight cases this solution was continued for the duration of the patient's intravenous fluid therapy. In the remaining cases, normal saline was the first solution given, but was discontinued in favor of 5 percent dextrose in 0.5 normal saline solution before the blood sugar level had fallen below 250 mg per 100 ml.

For all cases the average amount of fluid given in the first 24 hours was 6.9 liters with a range of 2.6 to 12.4 liters; the 48 hour average for all cases was 10.9 liters with a high of 21.5 and a low of 4.9.

In all 25 patient admissions supplemental potassium chloride was given intravenously; in all cases but one, not more than 20 mEq per hour was given. In one patient 60 mEq of potassium chloride was given in each of the first two hours after replacement therapy was begun. In this patient, rapid intravascular potassium loss was evidenced by a fall in the serum potassium level during the first six hours of therapy from an initial concentration of 8.0 mEq per liter to a low of 3.8 mEq per liter.

Potassium therapy was begun an average of 4.5 hours after admission, ranging from immediately to as late as 16 hours after admission. The average potassium ion replaced in the first 24 hours was 134 mEq (range 34 to 320 mEq), and in the first 48 hours was 159 mEq (range 34 to 400 mEq). In 16 cases all the supplemental potassium was given in the first 24 hours of therapy, oral feeding having begun by the end of that time.

Sodium bicarbonate was given intravenously in 19 cases. Bicarbonate therapy was begun on the average 2.7 hours after admission, but was begun immediately in five cases. An average of 142 mEq

TABLE 6.—*Evaluation of Therapy in Series of 25 Cases of Diabetic Ketoacidosis*

	<i>Number of Cases</i>	<i>Time (hrs.)</i>
Time to lower blood sugar.....	24	10 ( 3-36)
Time to correct acidosis.....	24	21 (10-60)
Time to eradicate ketonemia.....	14	18 ( 6-36)
Time to eradicate ketonuria.....	14	36 (11-71)

of bicarbonate was given in the first 24 hours, with a low of 45 mEq and a high of 352 mEq.

### *Results and Complications of Therapy*

To judge the effectiveness of correction of diabetic ketoacidosis in this series, four factors were examined to determine when correction occurred (Table 6). An arbitrary value of 20 mEq per liter for the carbon dioxide level was chosen as the criterion for correction of the metabolic acidosis. In 24 cases in which an adequate number of serial carbon dioxide determinations were performed to permit this analysis, it was found that the average time at which the first carbon dioxide level exceeded 20 mEq per liter was 21 hours, with a range of 10 to 60 hours. The average carbon dioxide level for this determination was 21.5 mEq per liter, thus demonstrating the nearness of the figure of 21 hours to the actual time at which the carbon dioxide level exceeded 20 mEq.

Similarly, an analysis was done to obtain the time at which the first blood sugar below 250 mg per 100 ml was determined. In the 24 cases in which blood sugar was above 250 mg per 100 ml on admission, the average time at which it went below 250 mg was 10 hours (range 3 to 36 hours). In this analysis the mean blood sugar level at this time was 178 mg per 100 ml; hence it is possible that it may have gone below 250 mg several hours earlier than the time at which it was determined.

Finally, in 14 cases serial determinations of serum and urine acetone were analyzed for the disappearance of ketone. It was found that the average time at which the reaction for serum acetone was found to be negative was 18 hours (range 6 to 36 hours) and the average time of negative reaction for urine acetone was 36 hours (range 12 to 72 hours).

Urine sugar content was not selected for analysis of this type because patients were generally allowed to spill varying amounts of glucose after correction of their metabolic and electrolyte defects.

The most commonly occurring complication in this series was a rapid fall in the serum potassium

level after the initiation of therapy. All 24 patients with serum potassium level determined at the time of admission had a decrease in potassium level during the first 24 hours of therapy. The average maximal fall in potassium concentration was 1.3 mEq per liter (range 0.3 to 4.2), and the average time of the maximal fall was 8.8 hours (range 3 to 18 hours) after admission. Five patients had serum potassium levels below the lower limit of normal (3.5 mEq per liter). The lowest levels recorded among these five patients were 1.6 mEq in one and 2.9 mEq in another.

Only one patient in this series had symptoms of hypokalemia; this patient had the lowest serum potassium level (3.3 mEq per liter) at the time of hospital admission and the lowest recorded serum potassium level in the entire series (1.6 mEq per liter). Sixteen hours after admission he began having pronounced muscle weakness and difficulty breathing; the deep tendon reflexes could scarcely be elicited and the electrocardiogram demonstrated decided S-T segment depression and prominent U waves. The patient was placed in a driving respirator and was given a digitalis preparation. This patient had received 80 mEq of potassium chloride before the onset of symptoms, and subsequently he was given 272 mEq at the end of 48 hours. The patient continued to improve as potassium replacement was carried out, and made an otherwise uneventful recovery.

Of additional relevance to the rapid fall seen in the serum potassium levels was the early administration of sodium bicarbonate. All five patients having recorded potassium levels below the lower limits of normal received sodium bicarbonate in the first two hours of therapy, and the two most seriously depleted patients received sodium bicarbonate during the first hour of treatment. The patient, described above, in whom symptoms of hypokalemia developed, received 44 mEq of bicarbonate intravenously at the time of hospital admission, and subsequently received a total of 156 mEq during the first 24 hours of treatment.

The second most common complication during the course of therapy was hypoglycemia from overdosage of insulin. Symptoms of hypoglycemia occurred in four patients; in three of them blood sugar levels determined at the time of symptoms were less than 60 mg per 100 ml. In two of the patients hypoglycemia occurred eight hours after admission, and in the other two it occurred 34 and 55 hours



after admission. All four patients responded promptly to the oral administration of orange juice.

One patient, admitted with blood pressure of 120/80 mm of mercury, became hypotensive six hours after admission, the blood pressure falling to 74/40 mm. This patient received 500 ml of a plasma expander over the ensuing 30 minutes, his blood pressure rose rapidly to normal levels, and he made an otherwise uneventful recovery.

Finally, in one patient of the three who had an in-dwelling urinary catheter in place for more than 12 hours a urinary tract infection developed. It responded well to removal of the catheter and antibiotic therapy.

## Discussion

This study examined the management of a group of diabetic patients from January 1964 through December 1968 with a discharge diagnosis of diabetic ketoacidosis treated in a 450-bed university hospital serving the Northern California area. All patients were referred to the hospital and were followed primarily by their private physicians before entry and at the time of discharge. Each patient was cared for by the medical housestaff on a general medical or pediatric ward with an attending physician and consultative supervision but with no uniform endocrine subspecialty supervision. The average age of the patients, the male:female ratio, the incidence of associated diabetic complications and the duration of the diabetes before the onset of ketoacidosis did not differ much from those reported in other series.<sup>7,8,9,10,11</sup> The patients may have been somewhat less severely ill than those reported by other investigators,<sup>1,9,10,12</sup> since only two of the patients had frank coma and ten had no recorded change in mental status.

This group of patients differs in several respects from previously reported series of patients with diabetic ketoacidosis. These differences include the fatality rate, incidence of infection and the overall results of therapy. The causes of these differences are difficult to assess in so small a series, but many factors must be considered: the particular group of patients referred to the Medical Center, the excellent care given most of the patients before hospital admission, the alertness of the housestaff caring for the patients, the availability of laboratory facilities, and the relative absence of diabetic complications in the patients studied. Although the relative importance of each of these factors cannot be quantitated in this review, their collective effect

on the excellent results of therapy cannot be overlooked.

The factors precipitating diabetic ketoacidosis are elusive and poorly understood. Certainly one of the most important precipitating causes in other series is infection, although the true incidence of documented infection is difficult to ascertain from many of these reports. In the present series the incidence of presumed infection in 13 cases of 25 cases (documented in eight instances) was higher than that reported for other series.<sup>1,7,8,9,10,11,12</sup> Dietary neglect and omission of insulin, which have been stressed by other observers as precipitating causes, were factors in only three of the patients.<sup>1,7-12</sup> In fact, several of the patients attempted to abort their attacks by increasing their insulin dosage. The frequency of nausea and vomiting with few positive abdominal findings was an impressive feature of this group of patients. Polyuria and polydipsia, although present in nine of the 25 cases, did not seem to be as reliable a symptom of ketoacidosis as Joslin<sup>9</sup> indicated it to be.

The clinical features of this group of patients at the time of hospital admission were not dissimilar from those described in other series. Dehydration was common (22 patients) as evidenced by dryness of skin, tongue and mucous membranes, and decreased skin turgor. Although neurologic complications were rare in these patients, 15 were classified as hyporeflexic on admission. Despite the high incidence of infection the absence of documented fever by oral temperature was striking, especially since only one of the patients had relative hypotension and none had frank shock. Although the absence of fever may in part be explained by the taking of oral temperatures in tachypneic patients, it is important to recognize that absence of fever cannot be taken to mean that infection is any the less likely in ketoacidosis.

The laboratory findings at the time of hospital admission are helpful in characterizing this group of patients. Only one patient was admitted in ketoacidosis with blood sugar less than 250 mg per 100 ml; 15 of the patients had normal serum potassium on admission and eight had an initial level above the normal range. Falsely low serum sodium due to large quantities of lipid in the plasma was not common. The striking increase in leukocyte count, even without obvious infection, was important. In fact, the group without infection had a slightly higher mean white cell count (20,000 per cu mm) than the group with documented infection (17,-



000 per cu mm). The striking increase in creatinine (mean 3.1 mg per 100 ml) on admission, which clearly reflected the severe dehydration, fell to normal in all cases after adequate hydration. Although dehydration and hypovolemia may lead to an increase in serum creatinine, the degree of elevation in these patients may also reflect underlying subclinical diabetic nephropathy.<sup>13</sup> The increased anion gap was probably due to the presence of ketoacids in the blood and relative renal insufficiency, although lactate accumulation may have been present as well. Seven of 22 patients on whom tracings were made had a normal electrocardiogram on admission. Fifteen had electrocardiographic abnormality which reverted to normal after correction of the metabolic and electrolyte imbalance.

The therapy of these patients was characterized generally by the use of relatively large doses of intravenous insulin (average 381 units in the first 24 hours), large amounts of fluid (average 6.9 liters in first 24 hours), early administration of potassium and the frequent use of sodium bicarbonate. With appropriate therapy acidosis was corrected in all cases within 21 hours, the blood sugar brought under control within 10 hours, the serum acetone corrected in 18 hours and the urine acetone the most delayed at 36 hours. Although bicarbonate therapy is recognized as an important adjunct in the treatment of diabetic ketoacidosis, we believe that caution should be used in the early administration of this drug. Because of the known effect of alkalization on lowering serum potassium levels, it is essential to monitor serum potassium levels carefully if bicarbonate therapy is employed. Experience with this group of patients suggested that most patients with diabetic ketoacidosis respond successfully to: (1) large amounts of hypotonic fluids (0.5 normal saline solution); (2) early administration of potassium intravenously; (3) frequent doses of regular insulin given intravenously (avoiding subcutaneous administration because of variable rates of absorption); and (4) avoidance of bicarbonate therapy unless acidosis is particularly severe.

The most common complication of therapy was a very rapid decrease in the serum potassium level after treatment was begun. All patients had a definite fall in serum potassium during therapy with

an average decrease of 1.3 mEq per liter occurring, on the average, 8.8 hours after admission. One case illustrated the potential hazard of early bicarbonate administration and delayed potassium therapy. The patient's serum potassium level decreased dramatically after bicarbonate, leading to severe muscle weakness and partial respiratory paralysis which greatly complicated management. Several observers have stressed the importance of careful monitoring of the serum potassium and avoidance of hypokalemia.<sup>14,15,16,17,18</sup> Fortunately only one of the patients in the present series had a low serum potassium level before therapy, a complication associated with a poor prognosis and difficulty in management.<sup>19</sup>

There were no examples of overt hyperosmolar coma,<sup>20</sup> lactic acidosis,<sup>21</sup> cerebral edema after therapy,<sup>22</sup> or severe insulin resistance encountered in this series.

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# Therapy of Primary Breast Cancer

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■ *Most breast cancers are multicentric in origin. They drain into two primary lymphatic depots—the axilla and internal mammary chain of nodes. The incidence of metastasis to the internal mammary nodes rises as the location of the primary tumor approaches to the sternal margin of the breast.*

*One hundred and thirty-seven patients primarily with in situ and non-infiltrating intraductal carcinoma were treated adequately by simple mastectomy and axillary dissection with preservation of the pectoral muscles.*

*All have remained free of disease. Infiltrating cancers arising in the lateral portion of the breast are best treated by radical mastectomy since they spread mainly to the axillary nodes. Medial and central infiltrating cancers have been treated by radical mastectomy with internal mammary resection, since they show a higher incidence of internal mammary metastasis. Seventy-two percent of 500 patients treated in this fashion survived at five years and 65 percent were clinically free of disease. A five-year salvage rate of 60 percent and a ten-year salvage rate of 50 percent were obtained in patients with only internal mammary node metastasis or in those with only axillary involvement. When both nodal areas were involved 43 percent remained free of disease at five years and 20 percent at ten years.*

*Mammography and biopsy of the contralateral breast at the time of radical mastectomy contributed to the detection of early localized breast cancer.*

CURRENT SURGICAL TREATMENT for primary breast cancer began in the 1890s with the introduction by Halstead and Willy Meyer of the now classical radical mastectomy. Until fairly recently this was considered to be the optimum procedure

for operable breast cancer. During the last two decades however, various modifications of the classical procedure have been introduced.

Of necessity, the primary curative attack on breast cancer continues to be a local one—a combination of surgical excision and x-radiation destruction of the primary tumor and its regional lymph node spread. Once disease becomes established beyond these confines, the patient is beyond cure by present means. Anatomical studies with

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dyes<sup>1</sup> have shown that, regardless of where the dye is injected, approximately three-quarters of the lymphatic drainage of the breast extends to the axilla and one-quarter to the internal mammary chain. Clinical studies,<sup>2</sup> however, demonstrate a higher incidence of metastasis to the internal mammary nodes when the primary tumor arises in the medial portion of the breast. On the basis of this clinical-anatomic concept<sup>3</sup> several operative procedures of varying extent are ideally suited for individual clinical settings.

The average infiltrating breast cancer arising in the outer portion of the breast spreads most frequently and at an early stage to the axillary lymph nodes. In this situation the classical radical mastectomy represents the surgical treatment of choice—supplemented by adequate supervoltage x-ray therapy to the peripheral lymphatic chain when axillary nodes are involved. In performing the classical radical mastectomy we have found several steps to be helpful. If there is any question regarding invasion of skin overlying the tumor mass, adequate margins of skin should be removed together with the operative specimen. In developing skin flaps the superficial fascia represents an ideal landmark. Dissection should always be made outside of the superficial fascia. This fascia separates the breast parenchyma from the subcutaneous fat and should always be included in the operative specimen. When approaching the axilla the clavicular and sternal heads of the pectoral major muscle are separated through the normal cleft which is easily found beneath the head of the clavicle medially. The sternal portion is excised from its tendinous attachment to the humerus. Dissection is then carried through the upper margin of the clavi-pectoral sheath, which is reflected downward exposing the axilla and facilitating a true mono bloc excision of the axillary content. We have found that in the lower portion of the operative field it is unnecessary to excise the rectus sheath below the costal margin. We usually clear the sheath from below and excise it from the level of the sixth intercostal interspace upward. This avoids diastasis recti and has not led to any increase in local recurrence.

Although we prefer to treat early localized lesions, we are not justified in being excessively selective in excluding patients with locally advanced lesions from a curative attack, provided that no evidence of systemic spread of disease is found on careful survey of the patient. Between

1945 and 1948 the great majority of patients at Memorial Hospital, New York, who had infiltrating breast cancer were treated by radical mastectomy; and although 62.5 percent had axillary node involvement, 57 percent survived and 50 percent were free of disease at five years. During the same interval, there was axillary node involvement in only 40 percent of early cases diagnosed by local excision of equivocal clinical lesions, and 74 percent were alive and 70 percent clinically free of disease at five years.

When a breast cancer is detected fortuitously at its earliest incipient stage—microscopic non-infiltrating or in situ lobular carcinoma—the main surgical effort should be directed toward complete removal of the entire breast parenchyma, since almost all breast cancers are multicentric in origin.<sup>4</sup> Patients with cancer at that early stage can be treated best by complete simple mastectomy together with axillary dissection with preservation of the pectoral muscles. The main advantage of this approach is the better cosmetic appearance resulting from preservation of the pectoral fold. We have performed more than 170 such procedures on suitable patients. All patients in this group were free of disease at the time of last report. (Three had died of other causes.)

We have applied the extended radical mastectomy<sup>5</sup> including excision of the internal mammary lymph nodes to patients with infiltrating cancers presenting in the medial and central portions of the breast, since the likelihood of metastasis to the internal mammary nodes increases as the location of the primary tumor approaches the sternal margin of the breast. More than 700 extended radical mastectomies have been done at the Memorial Hospital, concentrating on this selection. The incidence of internal mammary node metastasis has been high (33 percent) although only 50 percent of patients had axillary node involvement. Both axillary and internal mammary involvement were present in 25 percent of all patients in this group. At five years 72 percent were alive and 65 percent of all patients were clinically free of disease. At ten years 54 percent were alive and 51 percent were clinically free of disease. The most striking finding was that patients with only internal mammary node metastasis did as well as those with only axillary node metastasis when treated by the extended radical mastectomy.

In both groups, approximately 60 percent were free of disease at five years and 67 percent were



alive. At ten years the survival rate for both groups was 50 percent. Patients with internal mammary node metastasis can be salvaged by appropriate primary surgical therapy. Although the extended radical mastectomy is an excellent procedure when properly executed, it is more difficult technically than the classical radical mastectomy. Even in ideal circumstances morbidity is increased during the first two or three postoperative days. However, patients are discharged routinely eight or nine days following operation. Postoperative mortality within 30 days of operation is less than half of 1 percent. The classical operation supplemented by Cobalt 60 therapy to the internal mammary nodal area<sup>6</sup> affords an alternate method of treatment for patients with a high risk of internal mammary node metastasis in the average hospital in average circumstances. These patients receive a total dose of 4,500 to 5,000 rads tumor dose of CO 60, Cs 137 or electron beam therapy given over a five-week period through an anterior port covering the internal mammary chain and the base of the neck—the port extending from midsternum to the costochondral junctions and from the sixth rib below to about 2 cm above the clavicle above.

Optimum treatment of primary breast cancer can be attained through the rational application of all three operative procedures to appropriate clinical settings. Approximately two-thirds of our own patients with infiltrating cancers undergo radical mastectomy and the remaining third are treated by the extended procedure. All of the non-infiltrating cancers and a small number of very tiny infiltrating lesions arising in the tail of the breast have been treated adequately by the modified approach. Considering only infiltrating cancers, 93 percent of all patients seen by us with untreated breast cancer between 1957 and 1960 were considered operable. Approximately 50 percent of this group had positive axillary nodes. Seventy-five percent were living five years after operation, with local recurrence in only 2.5 percent. Of the group with inoperable disease, some of whom underwent palliative mastectomy for huge fungating tumors, none survived at five years and local recurrence was high. In the overall group of patients with infiltrating cancers, including the inoperable, 70 percent were living at five years. All patients treated for non-infiltrating or in situ cancer are free of disease.

In the treatment of infiltrating cancers with regional lymph node metastasis, we apply ag-

gressive supravoltage therapy to the peripheral nodal areas when metastatic nodes are found close to the margin of surgical excision, usually administering 4,500 rads (in air) over a five-week period. When huge tumors are present in the breast, particularly when invasion of the underlying pectoral fascia is found, aggressive therapy is also applied to the underlying chest wall because of the increased risk of spread through the intercostal lymphatics.

Early detection of breast cancer has contributed to the general, gradual improvement in survival of patients treated by conventional therapy. Mammography has been moderately helpful in this respect. Between 1961 and 1967, 3,000 of our patients had x-ray mammography as part of their work-up. In this group we were influenced by suspicious roentgenographic findings alone to operate upon 28 patients. In these 28 patients 14 cancers were found, nine in situ and five infiltrating. During the same period we operated upon 28 other patients whose mammograms were completely negative and found 21 infiltrating and seven in situ cancers. In the great majority of patients mammography did not affect our decision concerning primary therapy of the patient. Although mammography has been helpful in detecting some early breast cancers before they were apparent clinically, it is not a reliable diagnostic method. A negative mammogram should be disregarded in the presence of suspicious clinical findings.

We have become increasingly aware of the bilaterality of breast cancer. Some time ago in evaluating our ten-year survival rate in patients undergoing extended radical mastectomy, we were surprised to note that in 9 percent of patients treated by this method a primary cancer had developed in the opposite breast within ten years of the initial operation. Since then we have carried out biopsy of the opposite breast with increasing frequency at the time of mastectomy; and now at the time of mastectomy for a proved breast cancer we routinely perform biopsy of generous specimens of the opposite breast.<sup>7</sup> Most often minimal thickenings or areas considered suspicious by mammography are excised widely. Occasionally generous random biopsy specimens of the mirror image of the proved cancer as well as the upper outer quadrant of the opposite breast are examined in an effort to detect occult lesions. Bilateral breast cancer has been demonstrated in 16 percent of our own patients—6 percent asynchronous and 10 per-

cent simultaneous. Simultaneous biopsy of the opposite breast has detected cancer at a much earlier stage than was noted in patients who had had radical mastectomy of one breast and then were operated upon after minimal signs appeared in the remaining breast. In the simultaneous group only one patient out of 15 with infiltrating breast cancer in the opposite breast had positive axillary nodes and 60 percent of cancers in the opposite breast were at the non-infiltrating stage. By contrast, in the group which had undergone previous mastectomy, 23 percent of those with infiltrating cancers had positive axillary nodes and only 28 percent of the lesions found in the second breast were at the in situ stage. When carcinoma is found in both breasts simultaneous bilateral mastectomy is carried out, the extent of each mastectomy depending upon the clinical pathological setting in each breast. The salvage rate of these patients is comparable to that of patients with unilateral breast cancer.

Some locally recurrent breast cancers are still curable by<sup>8</sup> aggressive x-ray therapy or radical surgical excision. Parasternal chest wall recurrence arising from metastatic internal mammary nodes, or solitary recurrence in the skin flaps or in the axilla often represents direct extension of carcino-

ma from the primary tumor and can occur without the presence of concomitant systemic spread. Approximately 18 percent of patients with a parasternal recurrence treated by full thickness resection of the chest wall with primary closure have remained free of disease for long terms, some for as long as 17 years, following the secondary excision.

Current systemic therapy is at best palliative, uncertain and temporary in nature. Since the patient's only opportunity for permanent cure is through successful primary therapy, current refinements in early diagnosis and primary treatment must be utilized to the utmost if we are to improve our salvage of patients with breast cancer.

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#### ARRHYTHMIA DURING CRITICAL ILLNESS

"I believe unrecognized coronary disease is a major cause of the disastrous arrhythmias occurring during a critical illness. Among the American population there is a certain subpopulation at risk of sudden death. These are people who develop coronary atherosclerosis rather silently, who don't have much in the way of symptoms, who have an irritable myocardium, and who are prone to die suddenly. I believe that a certain number of these people at risk die during critical illness. They develop bacterial pneumonia or any serious disease and then die suddenly because of pre-existing coronary disease. It's possible that the illness they develop is an inter-current event and they would have died a few months later quite suddenly.

"So if a patient with a critical illness mysteriously develops an arrhythmia, the thing to do is to consider that he also has coronary disease and to give him the sort of care we think is part of coronary care for acute myocardial infarction."

—DAVID H. BLANKENHORN, M.D., Los Angeles  
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# Skull Injury From Stoning

## In Western Samoa and In History

CHARLES S. JUDD, JR., M.D., *San Francisco*

"And David put his hand in his bag, and took thence a stone, and slang it, and smote the Philistine in his forehead, that the stone sunk into his forehead; and he fell upon his face to the earth."

I SAMUEL, 17:49.

THE INCIDENCE OF compound depressed skull fractures has changed little over many centuries. Consequent originally upon acts of human antagonism, or from accidents, these fractures result similarly today from such practices as rock-throwing, on some of our university campuses among other places. Descriptions of ancient treatment, including trephining, reveal that the old methods effected remarkable results without the benefit of modern surgical adjuvants.

The usual small agent causing these fractures dispels its force locally without imparting much acceleration to the head. Dural penetration may occur, but brain damage is ordinarily superficial. Radial fracture lines join a curved line peripherally, representing the margin of the depressed area, and comminution occurs where the curvature of the skull changes noticeably.

Hemorrhage may result from a torn venous sinus or middle meningeal artery. Browder<sup>1</sup> warned against dislodgement of a fragment of bone depressed into a venous sinus, if sinus laceration is suspected, lest ingress of air cause air embolism, or profuse hemorrhage be brought about, or throm-

botic occlusion if one attempts dural repair over the sinus. Stöwsand and Geile said that late sequelae such as convulsions result from damage that occurs at the moment of trauma, and that elevation of depressed bone fragments and closure of the dura do not prevent them.<sup>2</sup> Gurdjian and Webster noted a mortality rate of 35 percent in persons who remain unconscious after injury.<sup>3</sup>

In compound depressed skull fracture, dirt or debris (potential infection) may be introduced with the in-driven fragments. DeBeaux reported removing fragments, boiling them and replacing them.<sup>4</sup> Bradford and Livingston used tantalum for immediate cranioplasty if they felt that the wound was "undeniably clean."<sup>5</sup> Watson-Jones warned, however, of the dangers of introducing metal to bone.<sup>6</sup> Gurdjian and Webster suggested delay in repair of a skull defect for a year if infection is present.<sup>3</sup> Sweet emphasized dural closure, even in the presence of bacterial contamination, to prevent brain herniation.<sup>7</sup> This closure may require a graft of fascia.

Twenty consecutive patients with compound depressed skull fracture came under my care recently (1966-1968) in Western Samoa, an independent Polynesian nation in the South Pacific. Stoning, the commonest form of Samoan aggression, caused the fractures in 12 cases, and domestic accidents such as the fall of a coconut caused the other eight. The initial injury caused temporary unconsciousness in 12 cases, and three patients showed neurological deficits. The bony depressions made

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by the injuries varied in size from 3 to 6.5 cm in diameter. In several there was decided comminution, and some wounds contained considerable dirt.

Roentgen examination, transfusions where necessary, tetanus prophylaxis, and the administration of antibiotics constituted initial management. Operative approach, usually under local anesthesia (lidocaine 1 percent), started with debridement of the scalp wound in all cases, and proceeded to elevation of the bony fragments. Sometimes manipulation of impacted fragments through a trephine hole in intact bone adjacent to the fracture site facilitated their dislodgement. In cases of pronounced comminution and dirty wounds, I removed and discarded fragments of bone, leaving a skull defect. The dura was sutured where torn, but grafting of dural defects was unnecessary. In one case, the fracture line crossed the groove of the middle meningeal artery, necessitating cauterization of this vessel and evacuation of an extradural hematoma through the skull defect. In several cases, I removed small amounts of macerated or devitalized brain. In six cases, significant skull defects resulted, three of which had to be closed later by tantalum cranioplasty.

Aside from slight residual hemiparesis in two cases and ptosis of an eyelid in a third, complications consisted of one localized superficial brain abscess, which occurred where fragments were left in the wound following elevation that was delayed for some hours after injury. Later treatment consisted of removal of fragments as sequestra from osteomyelitis, aspiration of the abscess, and the administration of penicillin, following which the patient recovered completely. There were no cases of post-traumatic epilepsy, on early follow-up, and no deaths in the series. In several instances, x-ray films taken many months after elevation of fragments showed complete fracture healing.

## Discussion

In speaking of accidents at a conference on head injuries in 1966, Walker referred to the host, the agent, and the environment.<sup>8</sup> In the above series, the *hosts* of these skull fractures were natives of a "developing" country, and the *environment* was a native village controlled by chiefs, without formal police. The natives suffered domestic injuries occurring in their daily activities in eight cases. In the other 12, however, the *agent* of injury was

stoning, done as an individual spontaneous act with intent to injure.

As a form of belligerence, stoning is not peculiar to primitive or isolated countries; one may observe it quite frequently today in American "confrontations." The stone as a weapon has not changed during many centuries, and the wounds it causes present a continuing challenge to the surgeon.

When the cave-dweller defended himself against an adversary, he reached instinctively for the closest tool or weapon, which was usually a stone. For aggression as well, man and other primates, even the baboon in Africa, used stones. Throwing a stone is definitive; the physical effort provides a release of emotion, and the results reveal themselves almost immediately.

From early times, stoning also acquired a more lawful and ritualistic sanction. Superstitious man threw a stone as an act of physical purgation to ward off a dangerous spirit. The thrower believed that evil resided in the stone itself.<sup>9</sup> Stoning appeared as a method of execution to avoid the pollution usually entailed by close contact with the guilty and dying man.<sup>9</sup> In Greek mythology, the gods tried Hermes for the murder of Argus. All the gods flung stones at him to free themselves from the pollution contracted by the bloodshed he had caused. Adopting this attitude, ancient Greeks stoned the wayside images of Hermes until eventually the heaps of stones came to be known as the *cairns of Hermes*.<sup>9</sup> Plato described the formal stoning of the executed body of an individual who had murdered a member of his family. Magistrates performed this act at a crossroads outside the town wall, in order to purify the city from the pollution it had acquired by the crime.<sup>9</sup> In Marseilles, a Greek colony that once suffered from a plague, a poor man offered himself as a scapegoat. For one year he was fed and treated well. Then the people led him through the streets, dressed in sacred garments and decked with holy branches, while prayers implored that all the evils of the populace might fall on his head. The people then cast him out or stoned him to death outside the city walls.<sup>9</sup>

Under Mosaic law, stoning was the ordinary and legal mode of capital punishment for various crimes that included idolatry, incest, bestiality, blasphemy, necromancy, cursing of a parent, violation of the sabbath, sacrifice of children to Moloch, rape of a betrothed virgin, being a "rebellious" son, prophesying falsely.<sup>10,11</sup> The stoning was a group action, but the witness of the crime usually cast

the first stone. Oxen were killed by stoning for goring a person to death. Moses and David were threatened with stoning, and the Jews wanted to stone Jesus for "blasphemy." The people of Lystra stoned Paul and abandoned him for dead. The stories of St. Stephen's death and the stoning of St. Sebastian are well known. One agitated group wanted to stone the entire city of Jerusalem.<sup>12</sup>

In our own day, group stoning occurred in the novel "Zorba the Greek," the scene of which was the island of Crete.<sup>13</sup> Shirley Jackson wrote an allegorical account of a ritual stoning in her story "The Lottery."<sup>14</sup>

Use of the sling is one of the ways in which stoning is elaborated. Observations by Bunkerah on its use in New Caledonia revealed that natives could knock down three out of five fruit bats at 60 yards, using a river-bed stone with a sling.<sup>15</sup> The Hawaiian slingstone was biconical, was 2.65 inches long and weighed 4.73 ounces, a little less than a baseball. The natives shaped it by rolling it between flat stones with motion to right and left as well as back and forth. Using a sling made from pandanus leaf, a skillful warrior hurled a stone so that it revolved on its axis like a rifle bullet.<sup>16</sup> In Peru the sling was made of woven wool.<sup>17</sup>

The usual target in stoning is the head, for it is known to be vulnerable and the assailant wishes to effect the maximum damage. Other examples in which the head serves as a target are the use of the "bean ball" in baseball, where the pitcher aims deliberately for the batter's head, and the circus booth activity where the object is to throw a ball or dart at an effigy of a head. Head damage caused by thrown stones occurs more frequently in the left parietal area, because the large majority of assailants are right-handed.

Examples of other weapons known to have caused compound depressed skull fractures may be found in the old culture of Peru.<sup>17</sup> The mace had a starshaped head of stone, 16.5 centimeters in diameter, and it often caused fatal impressed wounds. The Peruvian club was 28 inches in length and made of heavy wood. The axe had a haft 25 inches long and a narrow copper blade; it caused small thin depressed fractures. In a study of old Peruvian skulls, probably from warriors, Moodie noted one which showed seven depressed fractures of the occipital and parietal areas, a smashed nose, and a huge opening in the left temporal area.<sup>17</sup>

With regard to classical references to skull fractures, one of the earliest sources is the Edwin Smith Papyrus of ancient Egypt, dated at 1600 BC, but probably much older.<sup>18</sup> Forty-seven of the 48 cases presented pertain to trauma, and in 27 cases the injury was to the head. One of four cases of compound depressed skull fractures was described as follows:

"Title: Instructions concerning a gaping wound in his head, smashing his skull.

"Examination: If thou examinest a man having a gaping wound in his head, penetrating to the bone, (and) smashing his skull; thou shouldst palpate his wound. Shouldst thou find that smash which is in his skull deep (and) sunken under thy fingers, while the swelling which is over it protrudes, he discharges blood from both his nostrils (and) both his ears, (and) he suffers with stiffness in his neck, so that he is unable to look at his two shoulders and his breast . . .

"Diagnosis: Thou shouldst say regarding him: 'One having a gaping wound in his head, penetrating to the bone, (and) smashing his skull, while he suffers with stiffness in his neck. An ailment not to be treated.'

"Treatment: Thou shalt not bind him (but) moor (him) at his mooring stakes, until the period of his injury passes by. . . ."<sup>18</sup>

In the foregoing report, the verdict of "an ailment not to be treated" denotes the severity of the case. One wonders whether the blood from the ears indicated a basilar skull fracture, and whether the stiff neck identified meningitis as a complication. The 69 glosses or explanatory notes, added by the scribe who copied the papyrus, suggest, however, that the descriptions perhaps should not be taken too literally. The papyrus records minimal conservative treatment for these injuries, and does not mention trephining.

The Hippocratic writings, from 400 BC, describe skull fractures, and remark that if untreated, they result in fever, wound changes, convulsions, and death.<sup>19</sup> The author pays careful attention to the location of the fracture, noting that the skull is thin at the bregma, weak at the temples, and strong in the occiput. He records the extent of the wound and how the victim sustained it. He notes the different effects of blunt heavy objects and sharp light weapons. He makes the observation of hair in the wound, and states that a right-sided wound produces convulsions on the left. A quotation describes depressed fractures:



"Such pieces of bone as are depressed from their natural position, either being broken off or chopped off to a considerable extent, are attended with less danger, provided the membrane be safe; and bones which are broken by numerous and broader fractures are still less dangerous and more easily extracted. And you must not trepan any of them, nor run any risks in attempting to extract the pieces of bone, until they rise up of their own accord, upon subsidence of the swelling . . . and the pieces of bone ascend, if one will get the wound to suppurate and make it clean as quickly as possible."<sup>19</sup>

Studies of trephined skulls from France, Peru, Melanesia and other places revealed that in some cases the holes were made for non-medical reasons, but that the procedure was often used in the management of depressed skull fractures as well. Russu and Bologna noted that the practice of trephining and the use of the stone sling occurred together.<sup>20</sup> Ford attributed the disappearance of the procedure in Melanesia to governmental prohibition of slingstone fights rather than suppression of native medical practice.<sup>21</sup> Fischer-Moller remarked that in areas where metallic weapons and helmets were used, trephining died out because the neck proved to be more vulnerable than the head for inflicting fatal injuries.<sup>22</sup>

Ford's study of Melanesian fractured skulls revealed that native trephining was used to relieve compression of the brain caused by depressed portions of bone or by hemorrhage. A description of a native operation is as follows:

"The scalp was reflected until the whole area of bone injury was uncovered. If a comminuted fracture was then found, the fragments were carefully removed, and in the case of obvious injury to the brain, hidden splinters sought. Then, by scraping with a sharp flake of flint or obsidian, sharpened shell, or shark's tooth, the projecting corners were removed from the margin of the opening until it assumed a round or elliptical shape. If the fracture was not comminuted, a round or oval hole was scraped over the center of the injured area. The scalp was then replaced and the wound dressed in various ways."<sup>21</sup>

One skull showed a very regular circular trephine hole, 1.75 centimeters in diameter, in the center of a depressed fracture area about 4.50 centimeters across. Healing of the margins revealed that the patient had survived many years.

Reference to classic medical literature reveals other instances of the use of trephining in the treatment of depressed fractures. Celsus, 25 BC to 37 AD, the Roman encyclopedist, described such therapy:

"But when the fractured edges have become interlocked, a hole should be made with a trepan at a finger's breath to one side, and from this two cuts should be made with the chisel to the fissure, in the form of the letter V, with the apex at the hole and the base at the fissure; but if the fissure is a long one, similar cuts should be made from a second hole. And thus there is no concealed cavity in that bone, and a way out is given freely to all harmful material within."<sup>23</sup>

Galen, in treating depressed fractures, used a *lenticular*, a knife-like instrument with a round button on the end of it.<sup>24</sup> The button was inserted between the bone and the dura mater, and the cutting edge was driven through the bone by tapping the back of the blade.

Paul of Aegina, about 700 AD, advocated exposure of a skull fracture by making an incision in the scalp in the form of an "X".<sup>25</sup> He stuffed wool into the ears of a patient "to avoid the noise of the perforation." In wedged fractures, to loosen the fragments, he used a perforator called an *abaptista*, a spear-shaped instrument with a globular ball a short way up the blade, which prevented dural penetration.

In 1540, Hans von Gersdorff developed a tripod for the elevation of depressed fractures.<sup>26</sup>

At the siege of Metz in 1552, Ambroise Paré trephined the skull of Monsieur de Pienne at the site of a depressed frontal fracture that had caused vomiting, aphasia, and tremors. In describing the result of the operation, Paré stated in his customary way, "I dressed him . . . and God cured him."<sup>27</sup>

Cushing's contribution in World War I formulated modern neurosurgical principles which continue to be applied in the treatment of compound depressed skull fractures.<sup>28,29</sup> He removed damaged bone intact in an *en bloc* resection of a segment of the skull. In bullet wounds, he detected in-driven fragments of bone or debris by catheter palpation rather than by the exploring finger. He removed necrotic brain, blood clot, and foreign bodies by suction, fragments of bone by fine forceps, and metal fragments by electromagnet. He recommended closure of the wound if it was less than 12 hours old, and left the scalp open in



late wounds. He used Carrel's wound irrigation with an antiseptic solution.

## Summary

Compound depressed fracture of the skull, a well-known entity from antiquity, continues to be a prominent component of the spectrum of head injuries. A consequence of military trauma as well as domestic accidents, it has long had a close association with stoning. The prognosis is often excellent, as borne out in the presentation of a small series of 20 cases from a Pacific Ocean country. A review of methods of treatment reveals that the use of basic principles such as elevation of fragments and trephining many centuries ago has persisted to the present day.

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## PAVING THE WAY FOR SERIAL STRABISMUS OPERATIONS

"When you start treating a child with strabismus in whom surgical treatment is obviously necessary, I think it's always wise to acquaint the parents with the fact that surgical treatment may be necessary in more than one stage. I don't think it's a good thing to say, 'I am afraid this operation is not quite adequate and I'll have to do another one.' Otherwise you get this sort of remark from the parents, 'Well, the first operation failed, so he had to do a second one.' I think it is much better to gradually work the child up to a good result rather than to try to do too much, overdo it, and then have to go back and 'unpick' it. No matter how good you may think you are at surgery, you never quite know the outcome of any operation for strabismus. . . . Therefore it's always wise to do something that will get you somewhere toward the right result, and then be prepared, if necessary, to do further surgery."

—T. KEITH LYLE, M.D., London

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# CASE REPORTS

## Jaccoud's Arthritis

### Post-Rheumatic Fever Complication — Not Rheumatoid Arthritis

EUGENE B. LEVIN, M.D., *Los Angeles*

IN 1869, JACCOUD<sup>1</sup> described an unusual case of deforming arthritis which occurred in a patient after frequent severe attacks of rheumatic fever. The deformities were mainly in the hands and were characterized by muscular atrophy with severe ulnar deviation and flexion at the metacarpal phalangeal joints.

By 1967, only 15<sup>2-10</sup> cases had been reported in the world literature. Opinions have varied from that described above to others supporting the concept that this condition is a variation of rheumatoid arthritis. The patient described below has had this condition for 35 years following rheumatic fever and, in addition, has had severe generalized psoriasis, without signs of psoriatic arthritis, for the past 24 years. Discussion of the findings in this case will support the concept that this condition and rheumatoid arthritis are different entities.

### Report of a Case

The patient is a 44-year-old woman who had two episodes of "St. Vitus' dance" at age 9. They were extremely mild and short-lived and did not

require admittance to a hospital. Not during that time nor in subsequent years did the patient ever have any episodes of joint pain or swelling. At age 20 she first became fully aware of the fact that her hands were deformed. She said that she was able to perform motions of almost every type with her hands except to type and play the piano or other musical instrument. Soon after she became aware of the deformity, extensive generalized psoriasis developed, and it has remained with her despite multiple forms of therapy.

At age 31, congestive heart failure developed during the seventh month of her first pregnancy. This was the first indication she had had of any cardiac abnormality.

She delivered her first child without difficulty after careful medical management. Seven years later, she became pregnant again. During the third month, congestive heart failure again developed. The baby was delivered by cesarean section almost at term. From that time until the present, there has been no change in her health. On a low sodium diet and digitalis, she has raised her children without difficulty.

There is no family history of arthritis of any type.

The pertinent physical findings were as follows: (1) Wide areas of scaly quiescent psoriasis were noted. The scalp and nails were extensively involved. (2) There was no apparent cardiac enlargement. The blood pressure was within normal limits. The point of maximum intensity was in the fifth interspace at the mid-clavicular line. There was no right ventricular tap or heave. The pulmonary second sound and the aortic second were equal. A faint thrill was palpated at the apex and a Grade II-III/VI diastolic murmur, without radiation, was heard in the same area. (3) Both hands were decidedly deformed, almost symmetrically. There was palmar flexion and extensive ulnar deviation at the metacarpal phalangeal joints. The long axis of the fingers could be straightened but not held in this position. Most motions of the

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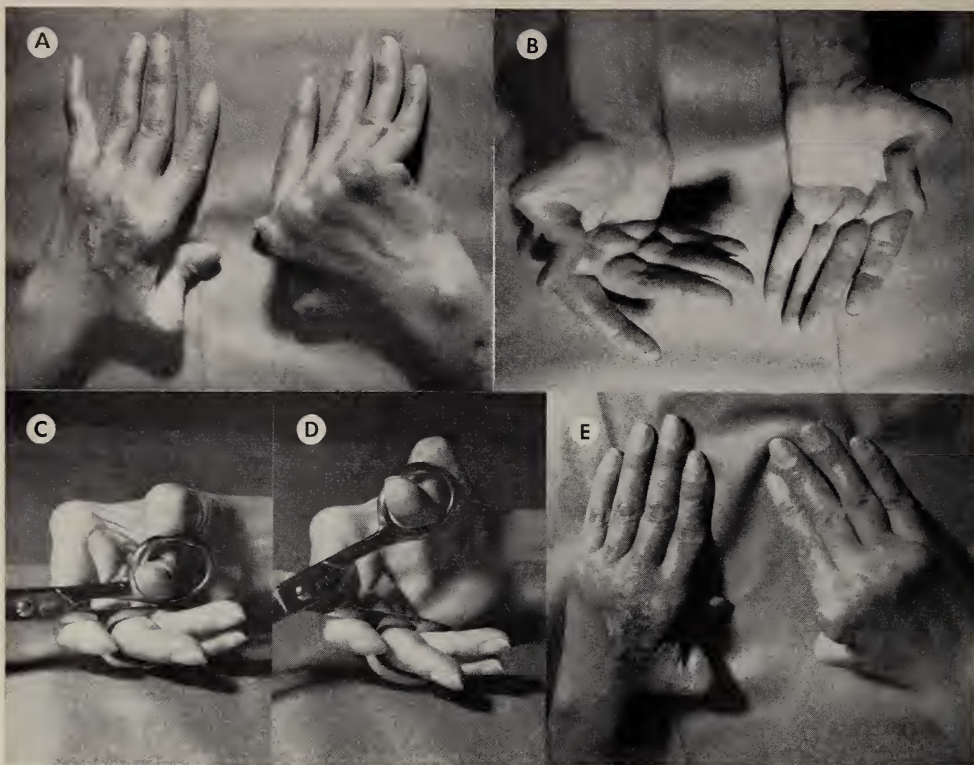


Figure 1.—*Top frames*, natural appearance of hands. Note the decided ulnar deviation of the fingers at the metacarpal phalangeal joints. There is no fusiform swelling of the proximal interphalangeal joints, but there is hyperextension present due to changes in the periarticular supporting structures. Note absence of psoriatic changes in nails. *Lower frames* show functioning of the thumb in opening and closing scissors; and, *lower right*, use of force straightens the ulnar deviation. (This position cannot be maintained spontaneously.)

fingers were present with the exception of total opposition (Figure 1).

On an x-ray film of the chest the cardiac silhouette was compatible with mitral stenosis (Figure 2). An electrocardiogram showed pulmonale p waves in leads II and III. Slight right ventricular strain was present (Figure 3). X-ray studies of the hands showed pronounced subluxation of the metacarpal phalangeal joints (Figure 4). There were no changes in any of the articular surfaces.

The erythrocyte sedimentation rate and serum uric acid content were within normal limits. The result of a test for rheumatoid factor was negative.

## Discussion

Burda and Sanders<sup>10</sup> recently reported a case of Jaccoud's arthritis in which there was a family history of rheumatoid arthritis and the patient had

a positive rheumatoid factor test. They concluded that this condition "represents an unusual variant of rheumatoid arthritis rather than a distinct complication of rheumatic fever." The case herein reported and a majority of others in the literature support the view that this arthritis is distinctly a complication following rheumatic fever.

Bywaters<sup>4</sup> summarized the characteristics of Jaccoud's arthritis as follows:

- There is a history of severe rheumatic fever with repetitive or prolonged attacks, associated with heart disease, chorea and migratory polyarthritis.
- Recovery may be delayed and it is associated with stiffness in the metacarpal joints, which may clear or may cause deformities.
- The characteristic deformity appears to be periarticular, fascial and tendon fibrosis rather than synovitis.



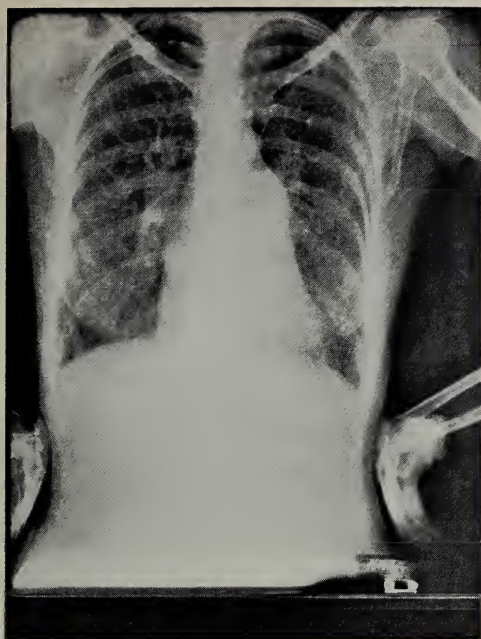


Figure 2.—X-ray film showing moderate pulmonary fibrosis. The heart is not enlarged. There is a prominence of the pulmonary conus and the suggestion of a double contour on the right cardiac border. These findings are in keeping with those seen in pure mitral stenosis.

- Deformity is due to flexion at the metacarpal phalangeal joints, associated with periarticular soft tissue swelling and ulnar deviation.
- Joint disease is inactive, with few or no symptoms, good functional capacity, normal sedimentation rate and a negative test for rheumatoid factor.
- X-ray studies rarely show the typical changes associated with rheumatoid arthritis (Figure 5).

The clinical features in the case herein reported are unique. The patient had extremely mild manifestations of rheumatic fever and had had two episodes of chorea. Later rheumatic heart disease with pure mitral stenosis was diagnosed. Never were there symptoms related to any of the joints, and deformity of the hands developed so gradually that the patient was not fully aware that it had occurred until she was adult. Deformity then remained static for 25 years despite the appearance of severe generalized psoriasis. She has almost complete functional use of her hands. X-ray films of the hands show only severe subluxation at the metacarpal phalangeal joints without stigmata of early or late rheumatoid arthritis. Finally, the

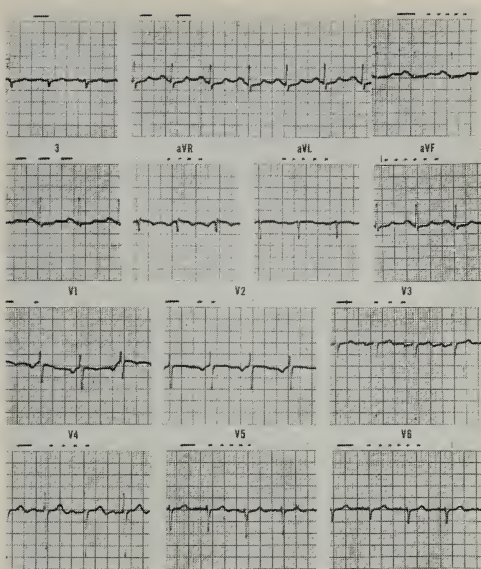


Figure 3.—The electrocardiogram is consistent with mitral stenosis. There is a right axis deviation. The p-waves in Leads II and III are consistent with pulmonic p-waves. The Prominent R in V<sub>1</sub> is in keeping with early right ventricular hypertrophy.

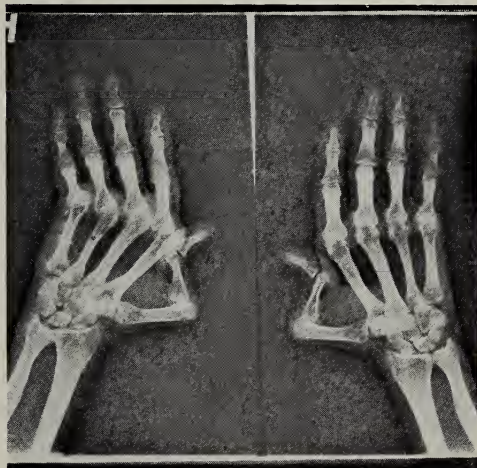


Figure 4.—Roentgenographic appearance of the hands is classical of Jaccoud's arthritis. Note there is no change in the articular surfaces of any joint. Subluxation of the thumbs bilaterally and of the metacarpal phalangeal joints is prominent feature. There are no changes in the carpal bones.

blood sedimentation rate is normal and a test for the rheumatoid factor was negative.



Figure 5.—X-ray films of two cases of old extensive rheumatoid arthritis with typical features—bony destruction along with articular changes at the interphalangeal joints, ulnar deviation, wrists decidedly involved.

In psoriatic arthritis, 70 percent of cases are indistinguishable clinically or roentgenographically from rheumatoid arthritis. In two-thirds of the remainder there is distal interphalangeal joint involvement and in one-third severely deforming arthritis with ankylosis and disorganization of many joints. The case here reported fell into none

of the above groups. Also, in the present case, unlike psoriatic arthropathy, arthritis developed before the skin lesions and there was no involvement of the nails.

It is clear that in this case arthritis followed rheumatic fever and was not a variant of rheumatoid arthritis. Although there are fewer than 20 reported cases, most investigators support the concept that Jaccoud's arthritis is a complication following rheumatoid fever.

## Summary

A case of Jaccoud's arthritis, following chorea, associated with rheumatic heart disease with mitral stenosis and not characteristic of rheumatoid arthritis, is reported. This is the only reported case associated with generalized, non-arthritic psoriasis. From the clinical and roentgen features it was apparent that the arthritis in this case was a post-rheumatic fever complication and not a variant of rheumatoid arthritis.

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# The Pathogenesis of Diabetes Mellitus

## Possible Usefulness of Spontaneous Hyperglycemic Syndromes in Animals

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OVER THE LAST few decades, considerable progress has been made in understanding biochemical abnormalities associated with clinical diabetes, particularly with its more short-term manifestations. Further, with the advent of insulin and improved acute resuscitation techniques, the morbidity and mortality rates in patients with juvenile-onset ketotic diabetes have been greatly reduced. The development of oral hypoglycemic agents, such as sulfonylureas and biguanides, has similarly resulted in improved metabolic control of non-ketotic, maturity-onset diabetes. Despite these advances in therapy, however, indeed partly because of the implied extension of the duration of clinical observation, awareness of the unsatisfactory state of our understanding of other, more chronic and less clearly biochemical problems in diabetic patients has increased rather than decreased. Among these problems one might single out the relative influence of genetic endowment and environment; the more detailed and long-term natural history of the disease; the relationship between diabetes and obesity and that between juvenile-onset and maturity-onset diabetes; the natural history of the vascular and neurological abnormalities.

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What is the definition of diabetes mellitus? Despite the widely voiced dissatisfaction with definition in terms of blood glucose levels, diabetes still cannot be diagnosed today unless the blood glucose level in a given metabolic state exceeds the range of blood glucose levels observed in the general population in the same metabolic state. The definition of diabetes must therefore remain that of a disorder associated with hyperglycemia inappropriate to the prevailing metabolic situation. In pathogenetic terms, the definition most frequently encountered is that of a condition resulting from "absolute or relative insulin lack." The latter part of this definition implies inadequate insulin effectiveness and is invoked to cover such findings in diabetes as the presence of high levels of serum insulin-like reactivity,<sup>1</sup> tissue resistance to insulin,<sup>2</sup> circulating antagonists to insulin<sup>3-5</sup> and synthesis and release of an abnormal insulin.<sup>6</sup> This pathogenetic definition may also be stretched to include abnormal patterns of insulin release.<sup>1,7,8</sup> It does not, as yet, suggest the cause of the "absolute or relative anomaly," nor the relation of this anomaly to most of the unexplained aspects of the disease which have been mentioned above.

Although students of the physiopathology of disease naturally prefer to consider single pathogenetic causes for any one disease, it is quite evident that different genotypic errors may produce entirely similar phenotypic diseases, as best illustrated, perhaps, by the different types of glycogen



TABLE 1.—*Syndromes Associated with Inappropriate Hyperglycemia and/or Obesity in Mice (Mus Musculus).*

Name	Gene symbol(s)	Transmission	Type Diabetes MOD* JOD†	Obesity	References
Yellow and variants	A <sup>y</sup> , A <sup>vy</sup> , A <sup>lv</sup>	Autosomal dominant	++	++	12, 13, 68, 69, 70, 71
Obese	ob	Autosomal recessive	++	++	12, 13, 45, 57, 58, 72, 73
Adipose	ad	Autosomal recessive	++	++	12, 74, 75
Diabetes	db	Autosomal recessive	++	+	12, 13, 76, 77
New Zealand obese (NZO)		Inbred strain—polygenic	+	++	12, 13, 58, 78, 79
KK		Inbred strain—polygenic	+	+	12, 13, 80
C3Hf <sub>x</sub> IF (Wellesley)		Offspring of two inbred strains—certainly polygenic	+	++	12, 13, 81

\*MOD = "Maturity-onset diabetes type."

†JOD = "Juvenile-onset diabetes type."

TABLE 2.—*Syndromes Associated with Inappropriate Hyperglycaemia and/or Obesity in Rodents Other Than Mice.*

Species	Transmission	Type Diabetes MOD* JOD†	Obesity	References
Acomys cahirinus (spiny mouse)		++ +	+	12, 13, 82, 83, 84
Genomys talarum (tuco-tuco)		++	+	12, 85
Psammomys obesus (sand rat)		++ +	+	12, 13, 46, 86, 87
Cricetus griseus (Chinese hamster)	Polygenic	++ +	—	12, 13, 88, 89
Fatty rat	Autosomal recessive	— —	++	12, 90

\*MOD = "Maturity-onset diabetes type."

†JOD = "Juvenile-onset diabetes type."

storage diseases. Although it was initially thought that glycogen storage disease may be a single entity, it was subsequently established that increased glycogen storage in different tissues may result from a variety of distinct and discrete enzymatic defects.

Alternatively, differences in the environment may either enhance or tend to obscure the presence of a genotypic lesion capable of producing disease, as illustrated by the considerable influence of prevailing dietary customs or, more directly, availability of food on the prevalence of diabetes mellitus in man. Since it is impossible to control genetic background in human populations and very difficult to control chronic environmental conditions, it unfortunately follows that the practical obstacles to a full definition of the factors involved in the pathogenesis of human diabetes may prove insurmountable. We have become intensely interested, therefore, in a possible escape from this deadlock through investigation of spontaneous diabetes and related disorders in animals. Here, genetics and environment may be perfectly and separately controlled, the natural history of the syndromes may be studied in minute detail and, in the case of the smaller rodents, many generations may be studied over relatively short periods. Indeed, we consider it already a significant contribution to our concept of human diabetes mellitus to realize that a similar disorder has been observed

in a great many mammals, including most domestic animals, but also such species as the dolphin,<sup>9</sup> fox,<sup>10</sup> and hippopotamus.<sup>11</sup>

The diabetic syndromes most likely to be of interest to research workers, of course, are the by now numerous ones described in small rodents and listed in Tables 1 and 2. In the remainder of this paper we should like to consider some of the more puzzling aspects of human diabetes and, where possible, to indicate animal models of spontaneous diabetes which have already contributed or may yet contribute to the better understanding of diabetic syndromes in general.

Although we shall refer to specific published reports in a number of instances, more general reference is made here to a recent and quite complete review,<sup>12</sup> as well as to a special symposium issue specifically concerned with spontaneous diabetes in laboratory animals.<sup>13</sup> We of course recognize that diabetes induced experimentally in laboratory animals such as that resulting from alloxan<sup>14,15</sup> or streptozotocin,<sup>16-18</sup> or that induced immunologically<sup>19-21</sup> provides additional useful models for metabolic disturbances associated with some forms of human diabetes, particularly juvenile-onset diabetes, but we do not intend to give detailed consideration to experimentally induced animal diabetes in this paper.

## Heredity and Diabetes

It is generally agreed that a tendency to the development of human diabetes may be inherited. It is not known, however, whether all cases of human diabetes entail an inherited component, nor is the nature of the genetic lesion or the mode of its transmission securely known. Until relatively recently, most prevalence studies in diabetic families were interpreted as suggesting transmission as a somatic recessive gene, with irregularities accounted for by "variable penetrance."<sup>22</sup> Major support for this view was derived from the greater concordance of manifest diabetes among monozygotic than among dizygotic twin pairs.<sup>23</sup> Despite this evidence, however, recent studies have emphasized that it is impossible to distinguish between a recessive characteristic with "varying penetrance" and polygenic control of a physiologic entity.<sup>24,25</sup> The difficulty is particularly great, when the age at which the phenotypic expression can be diagnosed is variable and when the probable overall penetrance is low. Both circumstances apply to diabetes and we must conclude today that the assumption of a somatic recessive mode of inheritance for human diabetes mellitus was premature. A polygenic mode of inheritance cannot be excluded. Indeed, a number of recent observations suggest that heritability of diabetes is polygenic and, in particular, different for youth-onset and maturity-onset diabetes. Thus, parents in whom diabetes developed early in life have been reported to have a greater proportion of diabetic children than parents with later development of the disease.<sup>26</sup> Since the tendencies toward the development of either type of diabetes generally occur in the same families, the observation suggests a possible additional genetic factor present only in the youth-onset type. Another complicating feature is the evident frequent coexistence and mutual influence of diabetes and obesity, which itself may have an inherited component.<sup>27</sup> A recent study in twins suggests that different genetic factors control simple glucose intolerance (chemical diabetes) and the transition from the chemical to the overt form of the disease.<sup>25</sup> Thus, the view which is now gaining acceptance considers human diabetes mellitus as a disorder of which the heritable component is polygenic, with the additional complicating feature that the phenotypic expression of one or several of the genes involved is likely to be conditioned by environmental factors, as we shall discuss later.

What does spontaneous diabetes in laboratory animals contribute to our understanding of heredity and diabetes? As seen in Tables 1 and 2, inappropriate hyperglycemia clearly is a genetically controlled abnormality and the precise mode of inheritance of the defect has been established in several syndromes of mice and in that of the Chinese hamster. Tendency to develop inappropriate hyperglycemia appears to be inherited as a dominant trait in yellow obese mice, as a recessive trait in *dbdb*, *obob* and *adad* mice, while it is probably polygenic in the inbred KK and NZO strains of mice, certainly polygenic in the C3HfXI hybrids and in diabetic Chinese hamsters. The polygenic nature of the defect is most directly apparent in the C3HfXI hybrids, since colonies of neither inbred parent strain tend to inappropriate hyperglycemia, while the anomaly suddenly appears in a large proportion of the offspring resulting from matings of the two strains. Clearly the major observation here is that inappropriate hyperglycemia may result not from one but from several distinct mutations, some of which may be transmitted as a dominant and others as a recessive trait. In addition, inappropriate hyperglycemia may be selected from mixed genetic material through inbreeding, and considerable evidence suggests that the syndromes so selected are of polygenic origin.

Although support for all concepts of human inheritance of the tendency to diabetes may thus be found in laboratory animals, we would like to suggest that the existence of human diabetes mellitus for as long as written records exist, as well as the surprisingly similar prevalence under similar environmental conditions in racially, and geographically distinct populations, support a polygenic rather than a mutational, monogenic origin in man.

## Environment and Diabetes

If a genetic component contributing to the pathogenesis of diabetes is an accepted fact, it is equally unquestioned that environmental factors are also significantly involved. The environment certainly modifies the duration of the time in which the tendency toward development of diabetes remains latent and thus influences what is described as the "penetrance" of the diabetic genotype. Among environmental factors, diet and physical exercise are probably of special importance, as well demonstrated by the reduction in the incidence of diabetes in Europe during and immediately follow-



ing the Second World War.<sup>28</sup> It is interesting to recall that Bouchardat<sup>29</sup> had commented extensively on the decrease in the prevalence of diabetes during the prolonged siege of Paris in the Franco-Prussian war of 1870. Such observations clearly establish that, given a particular genotype, the prevalence of the overt disorder may be altered by environmental changes.

Considerable interest has been centered on attempting to analyze the relative roles of environment and heredity through population surveys among different racial groups and in widely varying geographic locations.<sup>30-35</sup> Two types of results have been obtained. First, in populations with reasonably long-term stability of environmental conditions, the prevalence rates for inappropriate hyperglycemia have been remarkably similar throughout the world, with an average prevalence of overt diabetes of 1 to 1.5 percent, and an average prevalence of chemical diabetes in the neighborhood of 6 percent in representative population samples. Prevalences as high as 16 percent have been reported in population samples limited to persons aged 50 years or more.<sup>36</sup> As already mentioned with relation to heredity, these results suggest that genotypes favoring the development of diabetes are not preferentially associated with race or differing yet stable environmental conditions such as climate or individual foods.

The second type of result obtained, however, seems of special interest to us, even though it has been less frequently reported. An extremely low incidence of diabetes has been reported in Alaskan Eskimos<sup>37</sup> and in Athabaskan Indians<sup>38</sup> who are genetically unrelated but have similar environment and similar diet—high protein, low carbohydrate and moderate fat. Conversely, an exceptionally high incidence of diabetes, and also of obesity, as we shall discuss later, has been observed in the Indian population of South African cities such as Durban,<sup>39</sup> in New Zealand Maoris,<sup>40,41</sup> and in the North American Seneca,<sup>42</sup> Cocopah<sup>43</sup> and Pima<sup>44</sup> Indian tribes. In this last instance, the incidence of abnormal glucose tolerance in those over 50 years of age has been reported to be well in excess of 50 percent. All of these populations use Caucasian type diets, often with a recent increase in refined carbohydrates and in fat. Furthermore, all of these population groups are characterized by a recent decrease in the amount of physical activity required to maintain not only survival but accept-

able living standards. It has been suggested by Neel<sup>45</sup> that in such populations the major environmental event may have been the sudden change from conditions preexisting over many generations and requiring hard physical work with overall restricted and irregular availability of food, to conditions of essentially unrestricted food availability throughout the year and greatly decreased need for physical activity. He suggested that, in such instances, diabetes mellitus might represent the detrimental aspect of a "thrifty" genotype unmasked by "progress." In other words, diabetes might represent failure of adaptation to the relatively sudden transition to a sedentary existence combined with relatively high caloric intake.

Although the applicability of such a concept is exceedingly difficult to prove, it is certainly interesting to find that some of the spontaneous syndromes of inappropriate hyperglycemia in animals provide a very neat fit. Zoologists have long known that many rodent species transferred from their wild environment to caged living conditions tend to become obese. This is particularly pronounced when the animals' normal habitat is the desert or semi-desertic, arid regions. More specifically, the inappropriate hyperglycemia associated with obesity, which is so characteristic a feature of sand rats transferred from the Egyptian desert to a laboratory environment, exhibits several features predicted by Neel's concept. Thus, diabetes is most severe in the animals directly transferred and in the very first generations raised in the laboratory, often associated with life-threatening ketosis. The hyperglycemic syndrome then tends to become milder and disappear in subsequent laboratory-raised generations. Even in the directly transferred animals, diabetes may be entirely prevented by simple manipulation of the diet.<sup>12,13,46,47</sup> Similar observations have been reported in the South American rodent tuco-tuco and in the Eastern Mediterranean spiny mouse, *Acomys cahirinus*, although the case for failure of adaptation as a principal cause of the high incidence of inappropriate hyperglycemia in the latter is much less strong.

More generally, an influence of the diet on the incidence and the severity of the syndromes of inappropriate hyperglycemia has been demonstrated in almost all animals listed in Tables 1 and 2. We shall discuss this further, when considering the association of diabetes and obesity.



TABLE 3.—*Features of the Clinical Course of Syndromes Associated with Inappropriate Hyperglycaemia in Rodents.* (This summary represents the authors' interpretation of the information available to date. When no symbol is shown, no pertinent information is known to the authors. When the symbol is surrounded by a single pair of parentheses, the anomaly has been reported as transient over several months; parentheses and brackets indicate transience over days or two to three weeks at most.)

Syndrome	Obesity	Elevated serum IRI	Hypersecretion of insulin	"Resistance" to insulin	Progression to keto acidosis
Yellow	+	+	+	+	—
Obese ( <i>obob</i> )	++	++	++	++	—
Adipose ( <i>adad</i> )	++				—
Diabetes ( <i>dbdb</i> )	+	[(+)]	+++	[(+)]	++
NZO mice	+	+	+	+	—
KK mice	+	+	+	+	—
C3HfXI hybrids	+	+	++	(++)	—
Spiny mice	+	++	+	+	+
Sand rats	+	(++)	++	(++)	+
Tuco-tuco	+				
Chinese hamster	—	[(+)]		[(+)]	++

We may conclude this section by stating that the observations available in animals with spontaneous hyperglycemic syndromes confirm the importance of environmental factors in controlling the rate or relative proportion of potentially diabetes-prone genotypes achieving clinically overt phenotypic expression. Before continuing, we should like to mention another type of environmental influence, that of the uterus on the fetus, derangement of which may be of special importance to subsequent development. Experimental hyperglycemia *in utero*, as well as for male germ cells, has been reported to influence the subsequent development of inappropriate hyperglycemia in the offspring.<sup>48</sup>

### Diabetes, Obesity and Hyperinsulinism

The relationship between obesity and maturity-onset diabetes has long been known but remains poorly understood. The prevalence of obesity in adult diabetes has been reported to be as high as 60 percent,<sup>49,50</sup> while the prevalence of impaired glucose tolerance in obesity has also been estimated around 60 percent.<sup>1,51</sup> Perhaps the most striking relationship recently emphasized between the two syndromes is that both are associated with anomalies of insulin secretion and or effectiveness. Fasting hyperinsulinism and gross relative hyperinsulinism in response to glucose or other stimuli are characteristically associated with obesity.<sup>1,52,53</sup> When diabetes and obesity occur together, the immunoreactive insulin response to glucose or other stimuli is less than in the non-diabetic obese, but may still be greater than that in non-obese and non-diabetic controls.<sup>1</sup> The coexistence of hyperinsulinism (as compared with the normal state)

with either hyperglycemia or normoglycemia implies relative ineffectiveness of the circulating immunoreactive insulin, and relative ineffectiveness of exogenous insulin has indeed been demonstrated in obesity and in maturity-onset diabetes.<sup>2,54</sup> Additional similarities are that both are more prevalent in times of plenty, and that both are associated with increased morbidity and shortened longevity, due in many instances to vascular diseases. Indeed, in the light of the discussion in the previous section, both obesity and diabetes might well be considered as different expressions of a failure of adaptation to increased availability of food and decreased need for physical exercise.

Although not an undisputed finding,<sup>1</sup> the ability to reverse at least partially the hyperinsulinism of obesity through weight reduction,<sup>53,55</sup> has led to the postulate that obesity acts as a further stress to persons genetically predisposed to diabetes, and thereby facilitates clinical expression of the diabetic tendency. The decreased responsiveness to insulin associated with the hyperinsulinism in obesity has been reported to be more pronounced for muscle than for adipose tissue,<sup>2</sup> although adipose tissue clearly also responds less to insulin with increasing obesity. The hyperinsulinism of obesity may therefore tend to relatively favor insulin action on adipose tissue and thus the further accumulation of fat.

The spontaneous animal models may prove particularly useful in the illustration of the relationship between obesity and diabetes. Syndromes in laboratory animals provide a spectrum going from diabetes without obesity in the Chinese hamster,

through various degrees of severity in the association of hyperglycemia and obesity, to the *fatty* mutation in the rat, where obesity is associated with hyperlipemia and hypercholesterolemia but carbohydrate intolerance is not seen (Tables 1 and 2). A summary of the authors' present interpretation of the available information on the clinical courses of all syndromes associated, at least at some point, with inappropriate hyperglycemia is shown in Table 3. Quite generally, the syndromes may be subdivided into three groups. The first of these comprises the severest forms of the hyperglycemic syndrome, associated with pronounced resistance to insulin action, modest obesity, and degeneration of more or less hypertrophic and hyperplastic B-cells of the islets of Langerhans (*dbdb* mice, spiny mice and sand rats). In some instances, obesity may be quite pronounced, but transient: It precedes the development of ketosis, which is then associated with weight loss. Severe ketosis may also develop in Chinese hamsters, but the clinical courses of this syndrome will be analyzed further on.

Inappropriate hyperglycemia is much more benign in the second and largest group of syndromes, characterized by more or less pronounced resistance to insulin action, modest to pronounced obesity, and quite decided evidence for hypersecretion of insulin and elevated serum IRI. When both obesity and resistance to insulin are most severe, there is very decided hyperplasia of the B-cells of the islets of Langerhans. This group comprises *obob*, yellow and most inbred strains of mice (NZO, KK and the C3HfXI hybrids). Characteristic of the group is the previously best known of all hyperglycemic syndromes in rodents, that associated with the *ob* mutation and previously referred to under the name "obese-hyperglycemic" syndrome. During the second half of the life expectancy of these animals, there may be not only lack of progression toward ketosis, but even significant regression.

A third category is required in this classification, even though at present it comprises only one syndrome, that in the Chinese hamster. This syndrome stands alone in that obesity never develops and in exhibiting courses of greatly varying severity or rate of progression or both. Prolonged equilibrium may be reached with intermittent, mild or severe glycosuria, and while progression to ketosis and death is more frequent in animals with severe, persistent glycosuria, it is not an inevitable sequel.

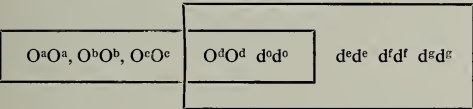
Except at the earliest stages, there is little evidence for hyperinsulinism or even increased secretion rates of the hormone. Pancreatic insulin is almost uniformly lower in hyperglycemic animals of all types than in normoglycemic ones. Several features of this variable and polygenic syndrome clearly derive from genetic similarities or dissimilarities. Thus, the incidence of ketosis in the offspring of matings between two frankly ketotic parents may approach 100 percent.<sup>56</sup>

At present and realizing fully that any conclusions reached at this stage are of necessity subject to periodic revision, it may be postulated that a possible sequence of events in most of the syndromes, with the exception of that in Chinese hamsters, would begin with decreased responsiveness to insulin as the primary event. This decreased responsiveness may be spontaneous (as in *obob* or *dbdb*) or diet-induced (as in sand rats or C3HfXI hybrids). In some instances, the decreased responsiveness to insulin may be more pronounced in certain tissues: Striated muscle appears to be particularly resistant to insulin action in *obob* or NZO mice<sup>57,58</sup> while hepatic tissue has been suggested as a preferential site of decreased insulin effectiveness for *dbdb* mice.<sup>59</sup> Decreased effectiveness of insulin is almost invariably associated with hyperinsulinemia. This may be either a very transient event, as in Chinese hamsters, or a rather long-lasting one, as in *obob* mice. Insulin resistance is usually most pronounced in adult or middle-aged animals, and may decrease later, as was particularly well illustrated by the studies of Westman<sup>60</sup> in the Swedish colony of *obob* mice and by Like et al<sup>13</sup> in the C3HfXI hybrids. Both hypertrophy and hyperplasia of the B-cells of the islets of Langerhans are frequently present at least at some point during the life history of most these syndromes, with the notable exception of the syndrome in Chinese hamsters and that in *dbdb* mice. In the last instance there is, however, excellent evidence for an early phase of attempted regeneration of islet cells from ductular epithelial cells and mitoses in the B-cells of these mice have been reported on by Like and Chick.<sup>61</sup> It would seem that, whenever hypertrophy and hyperplasia are sufficient in degree and can be maintained for sufficient periods to allow for a new equilibrium to be reached, near normalization or compensated diabetes together with hyperinsulinism is the result. Whenever the potential for hypertrophy and



hyperplasia is limited, either in degree or in duration, however, diabetes progresses and decompensation occurs.

In some of these syndromes in animals it is evident that a single somatic recessive mutation suffices to produce inappropriate hyperglycemia, hyperinsulinism and obesity, provided that environmental conditions include unlimited access to food and limited need for exercise. In other syndromes, the same association is based on polygenic traits and, as already discussed previously, we consider that the present weight of evidence favors a similar polygenic origin for human diabetes and also for human obesity. It may be warranted to speculate further that the high prevalence of obesity in diabetes, and of diabetes in obesity, in both animals and man, as well as the number of shared metabolic characteristics in both disorders, suggests the possibility that some genes may be common to both conditions. Some of these might control insulin biosynthesis, profiles of insulin release, capacity for hyperplasia of B-cells, and also ease of deposition or mobilization of lipids in adipose tissue, number of fat cells, and feeding habits. As represented diagrammatically below, some genes controlling these or similar phenotype traits might be characteristic for obesity only, others for inappropriate hyperglycemia only, while others still might be shared by both syndromes.



### Juvenile-Onset and Maturity-Onset Diabetes

Two major forms of primary diabetes, juvenile-onset and maturity-onset, are recognized clinically and in general are readily separable. However, the precise relationship between the two forms remains unclear. Both syndromes are associated with qualitatively similar abnormalities of intermediary metabolism, both exhibit a tendency to accelerated vascular disease, including microangiopathy, and both frequently occur within the same families and thus probably share some common genetic trait(s). Furthermore, and despite their names, both types of diabetes may occur at any age, and while the transformation of typical, ketosis-prone juvenile-onset diabetes into maturity-onset diabetes is exceptional, the transformation of

the maturity-onset syndrome into one bearing most of the characteristics of the juvenile-onset syndrome is not uncommon.<sup>62</sup>

Perhaps the clearest distinction between the two forms, is that recognized by Wrenshall 20 years ago<sup>63</sup>—that is, the almost complete absence of pancreatic insulin found at autopsy in juvenile diabetics (less than 10 percent of non-diabetic controls), compared with pancreatic insulin contents averaging better than 50 percent of non-diabetic levels in maturity onset diabetics, many values being well within the normal range. More recently, this same difference has been underlined by measurements of serum immunoreactive insulin levels and their response to insulinogenic stimuli. Although, as discussed in the preceding section, the *increased* insulinogenic response often seen in maturity-onset diabetes is most likely associated with the increased tendency to obesity of this syndrome, the response of serum immunoreactive insulin to insulinogenic stimuli in maturity-onset diabetics is quite generally greater than that in juvenile diabetic patients, where it is nearly always severely decreased.<sup>64</sup> Even this distinction, however, may be one of timing and degree rather than a truly differentiating, qualitative one, since the onset of juvenile diabetes is not infrequently preceded by hypoglycemia, suggesting at least transient hyperinsulinism.<sup>65</sup>

A reasonable present working hypothesis, in our opinion, would be that, while both syndromes are the likely result of one or several common anomalies, the differences between the two may result from different reactions to these anomalies as a consequence of genotypic or environmental individual differences or both. Among the anomalies common to both types of diabetes, it would seem reasonable to give first place to a probable anomaly of insulin biosynthesis or release, since some impairment of insulin release may be demonstrated in all types of diabetes, provided that comparison is with a suitable control group. Thus, as we have already seen, while the response of serum immunoreactive insulin to stimulation in obese diabetic patients may be greater than in persons who are not obese and do not have diabetes, it is still significantly smaller than in persons who do not have diabetes but are obese. Another, and possibly a still more important common anomaly is in the profile of insulin release: The earliest phase of release, after a given stimulus, is uniformly decreased in all diabetic persons tested so far,



TABLE 4.—*Structural Anomalies of B-Cells in Spontaneous Syndromes Associated with Inappropriate Hyperglycaemia in Rodents.* (This summary represents the authors' interpretation of the information available in the literature. When the interpretation is, so far, indirect only, the symbols are shown within parentheses. When no conclusion could be arrived at, the appropriate space is blank. Summary taken from Renold et al, Proceedings of second international Symposium on the Islets of Langerhans, Umea, 1969.)

	Y	obob	dbdb	NZO	KK	C <sub>3</sub> Hf	Sand rats	Spiny mice	Chinese hamsters
Hyperplasia	+	+	0	+	+	+	+	+	0
Mitoses			+						
Ductal proliferation			+					0	
"Mixed" cells			0					+	
Degranulation		+	+	(+)	+	+	+	+	+
Endoplasmic reticulum	(+)	(+)	+	(+)	+	+	+	+	+
Golgi	(+)	(+)	+	(+)	+	+	+	+	+
Mitochondrial anomalies			+			+	+	+	+
Glycogen			0			0	+	+	+
Hypergranulation								+	
Membrane-bound accumulations								+	+
Tickened B.M.								+	+
Degeneration (late)		0	+			0	+	+	+

whether of the juvenile or the mature type, whereas no such early decrease has been observed in obesity as such.<sup>13,51,55</sup> While this lesion may be distinctive and common to all diabetic persons, it clearly does not suffice to produce clinically overt diabetes, since the same abnormal profile of insulin release is seen in a significant proportion of normal persons as well.<sup>66</sup> Furthermore, several decades may separate the onset of clinical diabetes in the two members of homozygotic twin pairs,<sup>67</sup> even though the same initial abnormality of insulin release profile is observed in both from the very beginning.

In the spontaneous syndromes associated with inappropriate hyperglycemia in laboratory rodents, clinical courses reminiscent of either juvenile-onset or maturity-onset diabetes may be seen. Both types of syndromes have been described in Chinese hamsters, sand rats, spiny mice, and *dbdb* mice; also, although under rather special circumstances, in *obob* mice.<sup>68</sup> The different clinical courses which may be observed in all rodent syndromes have already been discussed in the section on obesity and hyperinsulinism, where it was emphasized that these courses may be influenced, in most syndromes, by environmental—mostly dietary—factors, while differences in the clinical course of any one syndrome may be clearly related to genetic factors, as it is in at least one syndrome, the polygenic syndrome in the Chinese hamster (L. Butler in 13). In addition, we should like to point out another very general similarity between the two syndromes in man and the several syndromes in laboratory rodents: Despite the manifest and decided genetic variations and variations in clinical

features, including greater or lesser dependence on environmental factors, all of the animal syndromes carefully studied so far do exhibit *some* anomaly of insulin-producing B-cells. Since the largest amount of information available concerns morphologic features, this statement is illustrated by the summary in Table 4, showing the structural anomalies of B-cells which have been described in spontaneous syndromes associated with inappropriate hyperglycemia. In particular, it may be noted that, of the four types of animals which may most characteristically develop ketotic diabetes, two (Chinese hamsters and *dbdb* mice) do not exhibit evidence of islet hyperplasia at any stage of the disorder while in the other two (spiny mice and sand rats) evidence develops of severe B-cell degeneration coincident with the more severe form of diabetes, despite preexisting hyperplasia of the insulin-producing cells.

Evidence for hypersecretion of immunoreactive insulin has been obtained in all known syndromes associated with inappropriate hyperglycemia in laboratory rodents, although this appeared to represent only a very transient event in some syndromes—as in *dbdb* mice or Chinese hamsters. Unfortunately, nothing is so far known to us as to the insulin secretion profile *in vivo* in any of the spontaneous animal syndromes.

### Diabetes and Vasculopathy

While the most desirable goals for students of the pathogenesis of diabetes mellitus remain those of a complete understanding of the mechanism producing the apparent anomaly of B-cell function and insulin secretion, and of the relationship of this anomaly and of genetic and environmental

factors to the acute and long-term metabolic and degenerative complications in patients with diabetes, most physicians would probably be willing to settle first for a clearer understanding of the particular relationship (if indeed there is one) of vasculopathy to absolute or relative insulin deficiency. Diabetic vasculopathy involves two major processes: (1) Increased severity, earlier occurrence and increased prevalence of atheromatous disorders of coronary and cerebral arteries, premature damage to large arteries, and (though less certainly) increased incidence of arteriosclerosis; (2) Microangiopathy, primarily associated with thickening of the capillary basement membranes in many tissues,<sup>91-94</sup> with specially disturbing consequences in the eyes and kidneys.

It is generally accepted that atheromatous lesions are increased in established diabetes,<sup>95,96</sup> while more recent studies suggest a similar damaging effect of even marginally impaired carbohydrate tolerance.<sup>97</sup> Since increased levels of serum cholesterol and triglycerides are also frequently associated with frank or borderline diabetes, it would seem reasonable to assume that vasculopathy of this type may, as suspected for atheromatous lesions in general have a metabolic origin and therefore benefit from dietary or other therapeutic measures resulting in decreased circulating levels of cholesterol and triglycerides. As to the spontaneous hyperglycemic syndromes in animals, it suffices to state here that with the exception of occasional reports of spontaneous atheromatous lesion in spiny mice,<sup>66</sup> no evidence bearing on their possible usefulness in the study of atheromatous lesions in diabetics has as yet become available.

Although microangiopathy has very occasionally been reported in other diseases, it undoubtedly remains the most specific and the most burdensome type of diabetic vasculopathy. This is particularly true for younger patients, a steadily increasing proportion of whom have detectable retinopathy or nephropathy after 10 to 15 years of diabetes, with a probable prevalence of 75 percent after 20 years. The major question concerning this vascular lesion is whether it is secondary to the metabolic anomalies of the diabetic state, or is another expression of the primary defect developing with, but independently of, these metabolic anomalies. In favor of the likely secondary relationship to metabolic anomalies are the increased vascular involvement with increased duration of

the disease, together with the observation that microangiopathy may occur in secondary diabetes, as in hemochromatosis. On the other hand, convincing evidence of a significant correlation of the severity of microangiopathy with the severity of the metabolic anomalies of diabetes is at best rare, and there still is today (nearly 50 years after the discovery of insulin) total lack of agreement as to the effectiveness of metabolic control in influencing the development and severity of these lesions. Furthermore, an extensive and most interesting recent report by Siperstein on skeletal muscle capillary basement membrane thickness measurements in a large series of overtly diabetic persons, suitable controls, and also in genetic suspects of diabetes, such as metabolically "normal" offspring of two diabetic parents,<sup>98</sup> has revealed a total absence of correlation between basement membrane thickening and duration of diabetes, as well as thickened capillary basement membranes in a significant percentage of as yet metabolically "normal" prediabetics. Siperstein concluded from his studies that microangiopathy may be an independent consequence of the primary genetic lesion in diabetes or represent the primary lesion, or even be an independent genetic lesion entirely. It should be noted, however, that agreement as to Siperstein's findings is not, as yet, general<sup>99\*</sup> and that, as we have discussed above, at least some endocrine-metabolic lesions have been observed in all identical twins of non-diabetic persons<sup>66</sup> whether any degree of inappropriate hyperglycemia could be demonstrated or not.

The information gained so far from animals with spontaneous inappropriate hyperglycemia is scanty. Since it has been suggested that microscopic changes in diabetic vessels may be secondary to the shunting of glucose metabolism to pathways not dependent on insulin, with excess or abnormal glycoprotein formation, it may be worth noting that the skin of diabetic Chinese hamsters, animals in which renal microangiopathy has been described, exhibit higher mucopolysaccharide and uronic acid content than do apparently normal controls.<sup>100</sup> In these animals, it has been reported that the incidence of vasculopathy is greater in individuals with diabetes induced by growth hormone and steroid administration than in spontaneously diabetic ones. Changes suggestive of renal microangiopathy have been reported in Chinese ham-

\*Also Pometta, Orci et al (in preparation).



sters, in *obob* and KK mice, as well as in spiny mice. In all these instances, however, it is as yet unclear whether the lesions are associated with diabetic metabolic decompensation or simply characterize quite generally these diabetes-prone strains or species, particularly with increasing age, regardless of the presence or absence of inappropriate hyperglycemia or other metabolic anomalies associated with diabetes. Clearly, the animals tending to spontaneous diabetes have not as yet proven helpful in shedding light on this all-important question which preoccupies diabetic patients and their physicians more than any other. However, the studies reported so far are only few and concern very small series of observations. We firmly believe that considerably more effort should be devoted to such studies, particularly since the preliminary evidence quoted does suggest that at least some lesions characterized by thickening of capillary basement membranes do occur in some tissues of small laboratory animals, perhaps more so in strains with tendency to develop diabetes. An important future object of study will be that of analyzing the consequences of induced experimental diabetes in comparable species or strains with and without spontaneous tendency to develop diabetes.

### Diabetes and Reproduction

One of the major, albeit less publicized concerns in diabetes is the incidence of impotence in the male, which may be as high as 25 percent in diabetic men between 30 and 34, and 50 percent in those between 50 and 54 years of age.<sup>101</sup> It has been suggested that this may be secondary to autonomic neuropathy, but the incidence of impotence in diabetic men with other evidence of autonomic neuropathy has been reported to be no higher than that in the general diabetic population.<sup>102</sup> The observation of decreased gonadotrophic secretion in a high proportion of impotent diabetics, and of anomalies in their sperm count and in testicular histology in one-third of such patients, suggests that hormonal factors may be involved. It is therefore interesting to note that similar histologic changes have been reported in diabetic Chinese hamsters<sup>89</sup> while *obob* mice exhibit both male and female hypogonadism, which can be improved by gonadotrophin administration and which does not appear to be secondary to either obesity or diabetes. Clearly, we may be dealing here with useful models for this important, yet still totally puzzling complication of human diabetes.

### Concluding Remarks

It is too early, of course, to reach a final conclusion about the true potential usefulness of spontaneous hyperglycemic syndromes in laboratory animals as it relates to our understanding of the pathogenesis of human diabetes mellitus. However, when one considers that the total amount of investigative effort which has so far been devoted to these spontaneous animal syndromes is, at best, a very small fraction of 1 percent of that devoted to investigating the pathogenesis of the disease in man, it is in fact surprising that partial conclusions on individual points can already be reached. We consider it likely, therefore, that much time and effort might be saved in the pursuit of the ultimate goal of complete understanding of pathogenesis, and therefore of potential prevention and improved treatment of human diabetes mellitus, by taking into consideration, at the planning stage of any investigative program, that which we have already—and, even more, that which we might yet learn from spontaneous inappropriate hyperglycemia in animals.

Thus, it is our opinion that the observations in animals already emphasize the need for utmost caution in considering any theory of diabetic pathogenesis based on a single and genetically simple anomaly. It is evident that, at least in mice, several individual genetic anomalies, each behaving as an individual gene, may each individually suffice to produce the phenotypic expression of a diabetes-like syndrome. It is also clear that, in other instances, phenotypic expression requires the combined presence of more than one gene—that is, that the diabetes-like syndrome may also be of polygenic origin. Finally, it is well established in animals that all spontaneous diabetes-like syndromes, whatever their genetic origin, may be considerably modified as to timing and severity of phenotypic expression through manipulation of the environment, particularly early in life, but also at later stages. The most recent and most comprehensive human genetic analyses are now reaching similar conclusions, but we should like to contend that such a conclusion would have been reached considerably earlier if the present information on the animal syndromes had been available 30 or 40 years ago.

It would seem unfortunate not to take advantage of our present knowledge for a much more comprehensive study of the genetic and environmental



factors contributing to the appearance and to the clinical course of inappropriate hyperglycemia in animals, since this knowledge might very likely allow us to approach the further study of human diabetes with more fully prepared working hypotheses, and with experimental designs allowing for sharper questions more likely to provide interpret-able answers.

We consider the preceding conclusion the primary and most important one at this stage. Additional, more fragmentary conclusions surely tend to confirm the need for combined study of the pathogenesis of diabetes mellitus with that of obesity, at least when concerned with diabetes of maturity-onset type. It would also seem that despite conceptual and methodological complexity the search for factors which decrease the sensitivity to insulin of tissues in general, or individual tissues in particular, should be continued. Finally, the observations in these spontaneous syndromes in animals confirm that the insulin-producing B-cell is involved at some stage in all of them, especially so in the more severe juvenile-onset syndromes. Thus we are encouraged to continue actively along the lines suggested by the concept put forward by Luft and Cerasi<sup>66</sup> while just as convinced of the need to search, just as actively, for the additional factor(s) so clearly required for diabetes mellitus to become the major and increasingly widespread clinical, public health and, above all, human problem that it is.

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# Antibiotics—Blessings and Curses

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JUST A QUARTER of a century ago, antibiotics came into widespread use. Probably no other class of drugs has had so profound an impact in a short time on the practice of medicine. Antibiotics have been and are both heroes and villains in human affairs.

At the outset of a discourse on a few of the blessings and some of the curses wrought by these drugs, it must be made clear that on the whole the position of antibiotics is secure in the medical armamentarium. A majority of bacterial infections can be treated easily, effectively and cheaply. Most patients receiving antimicrobial drugs recover from their illness, as well as from the untoward effects of the drugs. In fact the very success of antimicrobial drugs in curing infectious diseases may in time be looked upon as a curse. The dramatic reduction of mortality from infectious diseases is one of the main causes of the world's population explosion.

Without any doubt, antibiotics have given physicians far-reaching control over many common microbial diseases. Pneumococcus pneumonia can no longer be called the "captain of the men of death." Epidemic diseases of high mortality, such as plague or typhoid, have lost much of their dread. Infections like bacterial endocarditis, which had been uniformly fatal until 1940, now can frequently be cured. An excellent example of the powerful im-

pact of penicillin on sepsis caused by hemolytic streptococci can be seen in a comparison of similar outbreaks of childbed fever in 1927 and 1965. Before the antibiotic era, one-third of the patients died, whereas in 1965 all patients recovered without sequelae.<sup>1</sup> Such dramatic events highlight the blessing of effective antimicrobial therapy, and support the physician's faith in the ample benefits to be derived from antimicrobial drug treatment.

The last decade witnessed the emergence of drug-resistant microorganisms as a major cause of death, particularly in hospitals. First in staphylococcal disease and then in Gram-negative bacterial infections, physicians observed how one or another antimicrobial drug failed to cure the patient. Feeling threatened and searching for greater security in treatment, physicians increasingly employed mixtures of several antimicrobial agents. After all, it might seem reasonable to believe that if one drug is good, two should be better and three should just about cure everybody of everything. This search for security in treatment probably contributed greatly to the widespread, ill-advised use of antibiotic combinations. Perhaps the best explanation of this phenomenon has been provided by Mr. Charles Schulz, that leading observer of the American scene (Figure 1).

Osler wrote: "The desire to take medicine is one feature which distinguishes man . . . from his fellow creatures."<sup>2</sup> In the case of antimicrobial drugs this desire must be expressed to a physician who must prescribe the drug. Patients' requests, added to the

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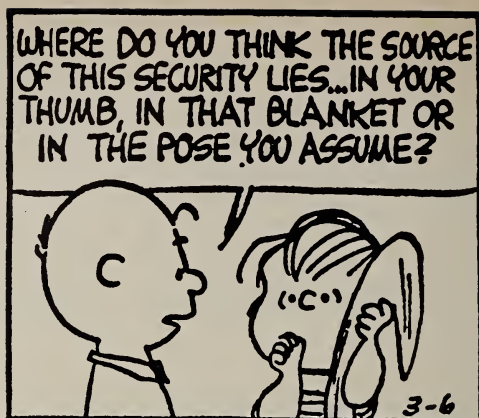


Figure 1.—(Reprinted by permission of Charles Schulz.)

physician's own faith that antimicrobial drugs are far more often helpful than harmful, probably contribute significantly to the consumption of antimicrobial drugs. Whatever the explanation, there can be no doubt that antimicrobial drugs are being prescribed by physicians on a large and ever increasing scale. In 1964, nearly half of all medicinal chemicals produced in the United States were antimicrobial drugs with a wholesale value of about \$386 million. For 1969, the figure was probably double that amount.

The overall effect of this large-scale use of antimicrobial drugs is difficult to evaluate. Undoubtedly, there is much iatrogenic disease produced, but there may also be hidden benefits. For instance, the great rarity of mastoiditis in children today may

be a result of the universal treatment of aching ears with antibiotics. Some cases of early osteomyelitis may be aborted by the treatment of suspected cellulitis with penicillin. The administration of large doses of penicillin for acute gonorrhea may sometimes eradicate coexistent undiagnosed early syphilis. In addition to these possible medical benefits, tangible pecuniary benefits accrue to medical journals. Journals have, in the front and in the back, pages of much better quality than those in the middle containing "scientific" material. In the front and back pages, the drug industry brings to the attention of doctors new drugs, often in glowing colors. Many medical journals could not be published at reasonable cost to the reader, were it not for advertising revenue.<sup>3</sup>



Figure 2.—An ancient representation of the persuasive visit of a medical educator sent by the Alpha Herb Company to the Greek physician, Thales. (From a potsherd discovered by E. Jawetz and H. Symmes.)

What is the effect of such advertising on the physician's choice of drugs? The ads are designed to evoke an instant association: When thinking of the possibility of infection—think *colossomycin*. Advertisements in journals, or by direct mail, probably succeed in conditioning physicians to a specific brand name. It seems probable that the physician's ultimate choice of drug is determined in part by ads, in part by conversations with other doctors and in part by hospital or medical meetings. But the Pharmaceutical Manufacturer's Association<sup>4</sup> avers that the most potent influence on the choice of drug is the friendly educator who is sent to us by the pharmaceutical house, the detail man (Figure 2). If that is true, then in view of the generally optimistic attitude of detail men, I consider it my obligation to mention a few of the major untoward effects which may be produced by antimicrobial drugs. These fall into several main categories: Hypersensitivity, toxicity, alteration of microbial flora, and evolution of microbial resistance.

### Hypersensitivity

Most antimicrobial drugs are not complete antigens. Either the drug molecule or one of its breakdown products attaches to host protein to form a complete antigen and to elicit various immune responses. These may range from mild fevers and skin rashes, gastrointestinal and serum-sickness-like allergic reactions, hemolytic phenomena and cholestatic hepatitis, to the most feared of all—acute anaphylactic shock. Anaphylaxis has occurred most frequently with the penicillins. In

many hospitals, adhesive tape strips with the words "allergic to penicillin" adorn many patients' charts. Curiously, some of these same patients are receiving penicillin, without any untoward effects. This paradox may be taken as an indication of our limited knowledge concerning penicillin allergy. The determination of anti-penicillin antibodies in the blood has virtually no predictive value, and skin tests with penicilloyl-polylysine, with intact penicillin, or with any of the available penicillin breakdown products, can predict only to a limited extent the risk of penicillin reaction in a given patient. Acute anaphylactic reactions seem to occur most commonly in dentists' or physicians' offices, when they are not anticipated, when facilities for their management are lacking, and when the indication for the injection of penicillin is questionable. Conversely, such reactions virtually never occur when the danger is anticipated, and when one is prepared to handle the emergency.

When cephalosporins were first introduced, it was believed that they could be administered to penicillin-sensitive persons with impunity, because their nucleus was sufficiently different from the penicillin nucleus to avoid allergic cross-reactions. This hope has not been entirely fulfilled: About 10 to 30 percent of penicillin-sensitive persons also react to cephalosporins.<sup>5</sup>

### Toxicity

Virtually all drugs exhibit direct toxicity of some kind for man and whenever a physician selects an antimicrobial drug for a given patient, he must weigh the possible benefits against the possible harm in the specific situation. If we draw a scale of toxic effects for antimicrobial drugs, we might place penicillin at one end and amphotericin at the other. Penicillin is virtually nontoxic for mammalian cells in most situations with the exceptions of central nervous system irritation by exceedingly high concentrations. Amphotericin, on the other hand, always evokes a variety of untoward side effects when therapeutically active doses are employed in the treatment of mycotic disease.

In his desire to anticipate toxic reactions, the physician may be helped by knowledge of specific host characteristics which greatly predispose to toxic reactions from antibiotics. A few examples may be mentioned. The extremes of age, infancy and old age are particularly important. In early in-

**BACTERIAL ENDOCARDITIS (MICROAEROPHILIC  
STREPTOCOCCUS) WITH MILD RENAL INSUFFICIENCY  
(SINGLE KIDNEY)**

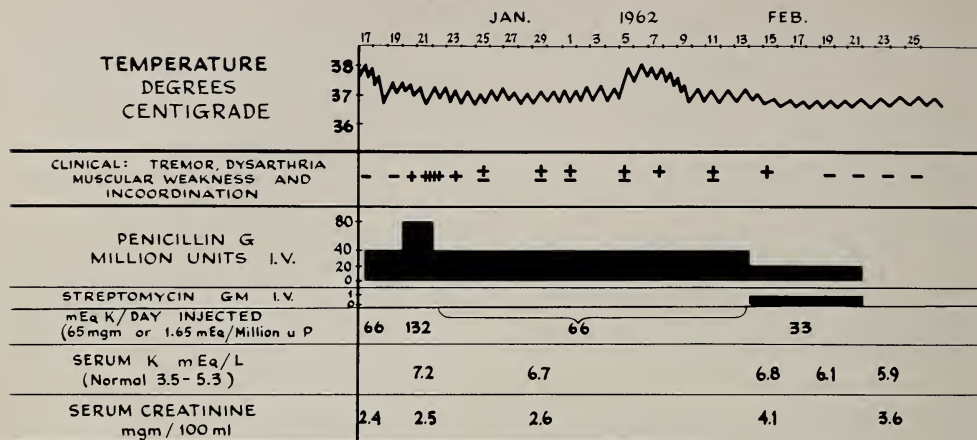


Chart 1.—Chart of a 70-year-old man who had a kidney removed one year previously and entered the hospital with typical bacterial endocarditis. The microaerophilic streptococcus isolated from the blood stream was only moderately sensitive to penicillin G. Treatment with penicillin G, 40 million units (24 grams) daily resulted in bactericidal activity in a serum dilution of 1:5. The dose of penicillin G was then increased to 80 million units (48 grams) a day. After one day of such continuous infusion the patient awoke with decided tremor, dysarthria, muscular weakness and incoordination without any localizing neurologic signs. Cerebral embolism was suspected, but a serum potassium level was 7.2 milliequivalents per liter (with 5.3 as the upper limit of normal) and the serum creatinine was 2.5 mg per ml. Acute potassium intoxication was diagnosed and the daily potassium injection was reduced from 132 mEq in 80 million units to half that amount in 40 million units penicillin G daily. The signs of potassium intoxication subsided and the bacterial endocarditis was eradicated on this regimen. (Reproduced with permission of Dr. F. Chamberlain.)

fancy, when renal function is as yet poorly developed, some antimicrobial drugs are not excreted promptly and may cumulate to toxic levels. In the first few days of life, the dosage of aminoglycosides and other drugs must be adjusted to avoid such toxic cumulation. In infants, liver function is immature. As a consequence, chloramphenicol is not conjugated with glucuronate (gluconyl transferase is deficient), the drug is not detoxified and may produce the highly lethal "gray syndrome."<sup>6</sup> Tetracyclines administered to a woman after mid-pregnancy, or to young children up to six years of age, tend to be deposited in rapidly growing bone tissue and tooth enamel. This results in depression of bone growth and in irregularities and staining of teeth.<sup>7</sup> Sulfonamides given to women late in pregnancy may produce kernicterus (bile-staining of basal ganglia) probably because sulfonamides displace bilirubin from binding sites on albumin, and the free bilirubin can pass membranes which are impermeable to albumin-bound bilirubin.

In old age a number of other problems prevail. Intramuscularly administered drugs are absorbed

irregularly. Renal function is often impaired and drug excretion is slowed. Drugs like streptomycin, kanamycin, vancomycin or the polymyxins may cumulate to high levels which further damage renal function, and which also may produce pronounced neurotoxic and ototoxic effects.

In all age groups, renal function is an important determinant of untoward drug effects.<sup>7</sup> In renal failure, many antimicrobial drugs which are normally excreted by glomerular filtration or tubular excretion (such as the group mentioned above, but also the tetracyclines and lincomycin) cumulate and are likely to produce toxic effects, unless the dose is drastically reduced or the interval between doses greatly increased. Several schemes for dosage adjustment in the face of renal insufficiency have been proposed.<sup>8</sup> By contrast, chloramphenicol and the erythromycins are handled independently of renal function and can be given in full dosage in renal failure. Certain drugs—for example, nitrofurantoin—are completely protein-bound after absorption, and must be separated from the protein carrier by tubular activity. In



renal failure this event may not take place, so that little or no nitrofurantoin reaches the urine. While penicillins rarely reach neurotoxic levels as a result of cumulation in renal failure, it is well to remember that each million units of penicillin G contains 1.7 milliequivalents of potassium. Inability to excrete this potassium in renal failure results in dramatic intoxication, as illustrated in Chart 1.

**G**enetic considerations may also permit some prediction of the likelihood of untoward drug reactions. In comparison with the majority of people, some ethnic groups are known to inactivate INH (isonicotinic acid hydrazide) very slowly by acetylation. As a result, such persons cumulate INH and polyneuritis may develop in spite of pyridoxine treatment. Reduction in the dose of INH is essential to eliminate iatrogenic neuritis in such persons.<sup>7,9</sup> In some racial groups, red blood cells exhibit a deficiency of glucose-6-phosphate dehydrogenase (G6PD), and are prone to undergo hemolysis. Such hemolytic reactions can be precipitated by the administration of sulfonamides, nitrofurantoin, chloramphenicol and other drugs, and can be avoided if the physician is aware of the special risk associated with the genetic defect.<sup>10</sup>

Abnormalities of developing red blood cells develop in every person ingesting chloramphenicol, 4 grams or more daily. This toxic effect is reversible. It is quite distinct from the greatly feared aplastic anemia, which may occur with small doses of chloramphenicol in rare individuals with a specific idiosyncrasy—probably an enzyme defect.<sup>11</sup>

As a last example, pregnancy should be mentioned. Relatively little is known about the possible harmful effects of antimicrobial agents on the fetus, but I have already alluded to such problems as sulfonamides causing kernicterus or tetracyclines causing bone defects. So many physiologic functions are altered in pregnancy that increased susceptibility to toxic effects of antimicrobial drugs is a good probability. The reported high hepatotoxicity of tetracyclines in pregnant women may serve as a warning example.<sup>12</sup>

### Alteration of Normal Flora, Suprainfection, Emergence of Resistance

The selection pressure of an antimicrobial drug manifests itself in several ways. It may suppress normal flora and thus may pave the way for the implantation and proliferation of organisms abnor-

mal for the particular body site. Such abnormal organisms may then cause disease. Example: A woman takes tetracycline for a urinary tract infection. The tetracycline suppresses normal vaginal flora, favors overgrowth by candida which then produce active vaginitis.

The selection pressure of drug also is unavoidable when a specific disease is being treated. Example: *Pneumococcus pneumoniae*, treated with penicillin, responds, but the penicillin favors overgrowth of Gram-negative bacteria in the upper respiratory tract. These organisms may then be aspirated and produce a suprainfection<sup>13</sup> in the lungs. The likelihood of this sequence will be reduced if only adequate amounts of drug are given for an adequate amount of time (rather than an excess in dose and time), and if host defenses are restored to normal as rapidly as possible.

The selection pressure of the drug will inevitably favor the survival of the most resistant bacteria in a population. In short order the resistant mutants prevail in the infectious process, and the drug treatment fails. Example: Staphylococcal endocarditis is being treated with erythromycin. Initially, there is clinical improvement, with suppression of the microbial population, but in four or five days erythromycin-resistant staphylococci have been selected and erythromycin treatment fails. The emergence of resistant mutants is a prominent reason why such drugs as erythromycin, novobiocin and streptomycin cannot be used as single drugs in the prolonged treatment of chronic infection.

**T**hese examples may serve to illustrate the production of iatrogenic disease as a result of the administration of antimicrobial drugs. They also bring up the general problem of "antimicrobial chemoprophylaxis." If antimicrobial drugs are good in the treatment of established infections, should they not be even better to prevent microbial infections? The reasoning seems compelling, but it is not quite correct. You *can* prevent infection by one specific microorganism if you employ a specific drug aimed at that microorganism. This is the basis of rational chemoprophylaxis. You *cannot* prevent all infections by many different organisms by using any one drug or drug combination — that is, you cannot ban the entire microbial world.

Examples of rational chemoprophylaxis are the administration of sufficient penicillin to prevent gonococcal or group A streptococcal infection. Ex-

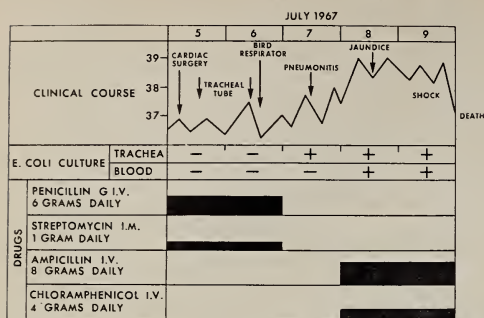


Chart 2.—Chart of a 53-year-old man in whom signs of congestive failure had developed abruptly several months earlier. Repeated studies revealed a probable tumor in the right atrium. At operation an atrial myxoma was removed without difficulty, but respiratory difficulties developed and an endotracheal tube was inserted and a respirator employed to improve ventilation. On the day of operation, penicillin and streptomycin were begun by parental injection "to prevent infection." Initial cultures of material from the trachea showed only normal flora. After two days on "prophylactic" antibiotics, *E. coli* was grown from tracheal aspirates and signs of pneumonitis developed. In spite of the administration of ampicillin and chloramphenicol in large doses, bacteremia with *E. coli* supervened, jaundice developed and the patient died in shock in spite of supportive treatment.

amples of irrational chemoprophylaxis are attempts to prevent possible wound infection by means of administering any drug after a simple surgical procedure such as herniorrhaphy.<sup>14</sup> But what about prevention of specific bacterial infections in elective surgical procedures—for example, in cardiomy? The risk of implanting a streptococcus viridans in damaged endothelium is very great. Therefore, many cardiac surgeons employ penicillin post-operatively. As a result, streptococcus viridans endocarditis virtually never occurs after operations on the heart, but other organisms do produce infection. Because staphylococci are greatly feared, methicillin is employed as "prophylaxis" to eliminate them. This in turn, favors the selection of a series of Gram-negative bacteria of increasingly greater drug resistance. The Gram-negative bacteria are currently the biggest offenders in post-surgical and other hospital infections. There can be no doubt that antimicrobial drugs, given with the best of intentions, favor these opportunistic organisms. A recent example is given in Chart 2.

Medicine is becoming constantly more aggressive. More and more daring procedures are undertaken to maintain life. The transplant patient, filled

with immunosuppressive drugs and corticosteroids, all too readily falls prey to his own endogenous microorganisms. Cytomegalovirus pneumonia, Candida sepsis, Pneumocystis pneumonia, Pseudomonas pneumonia and sepsis are common in such patients but are virtually unknown as primary diseases in medicine. The first heart transplant patient in the San Francisco Bay Area died with the fungus Aspergillus growing in the wall of the coronary artery of his new heart.<sup>15</sup> This fungus never produces disease in normal persons. At the time of his decline the patient was receiving four antimicrobial drugs and several immunosuppressants. Small wonder that Aspergillus had a chance of growing in tissues.

It is clearly not possible to interfere with progress in medicine. But as more and more procedures and drugs are used aggressively in medicine, it is urgently necessary that each physician in each case weigh the benefits (which in general are demonstrably many) against the risks. On November 17, 1952, the Hunterian Society (London) debated the proposition, "The continued advance in medicine will produce more problems than it solves." The proposition carried by 59 to 47.<sup>16</sup> The majority vote does not admonish us to avoid the "continued advance" but it does remind us anew of the vigil we must keep.

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## MEDICAL STAFF CONFERENCE

# Thyrotoxicosis and Pregnancy

*These discussions are selected from the weekly staff conferences in the Department of Medicine, University of California, San Francisco. Taken from transcripts, they are prepared by Drs. Martin J. Cline and Hibbard E. Williams, Associate Professors of Medicine, under the direction of Dr. Lloyd H. Smith, Jr., Professor of Medicine and Chairman of the Department of Medicine.*

DR. SMITH:\* This morning we are not going to talk about the medical condition of pregnancy per se, but about one of the possible complications, hyperthyroidism. Dr. Fitzgerald will present the case summary.

DR. FITZGERALD:† This was the first University of California admission for this 22-year-old white primagravida whose chief complaint was "thyroid trouble." She had been entirely well until March of this year, when she noticed a slight dysphagia for solids and liquids. The last normal menstrual period occurred in June. In July she noticed the gradual and progressive onset of increasing appetite, vomiting (which began as morning sickness, but which eventually occurred intermittently throughout the day), diarrhea, diaphoresis, anxiety, heat intolerance, diffuse muscle aches and wasting, and tachycardia with palpitations. She experienced an episode of blurred vision. She had recorded a 35-pound weight loss over the preceding seven months, despite increased appetite. In July the patient's physician told her that she had "big eyes." He obtained serum tests which showed increased thyroid function and confirmed her pregnancy with a urine study. The patient's past medical history and social history were noncontributory. Her family history was of interest in that one sister may be diabetic.

On initial examination the patient was thin and tremulous. The vital signs showed a pulse of 100 per minute with frequent extrasystoles, blood pressure within normal limits, respirations 16 per minute, temperature was 37°C (98.6°F). The skin was dry but there was no pretibial myxedema. Scattered spider angiomas were observed. Examination of the eyes revealed a prominent stare, lid lag, and mild exophthalmos. The patient was unable to wrinkle the forehead by elevation of the eyebrows. Extraocular movements and results of funduscopic examination were all within normal limits.

Examination of the neck revealed an enlarged thyroid gland weighing approximately 100 grams. The gland was tender and firm with a palpable systolic thrill and bruit. The chest was clear. The heart was not enlarged, but the point of maximum impulse was prominent and the rhythm was irregular with frequent extrasystoles and sinus tachycardia. There was a soft  $s_3$  gallop at the apex and a 2/6 soft ejection murmur heard best at the pulmonary area. There was no hepatosplenomegaly. The uterus was firm with the fundus palpable at the symphysis pubis. The muscle mass in the extremities was decreased and there was generalized muscle weakness which was greater proximally than distally. Neurologic examination was normal save for a fine tremor and symmetrically increased deep tendon reflexes.

Initial laboratory studies showed a hematocrit of 37 percent with a white blood count of 5,500

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per cu mm and a predominance of neutrophils in the differential. Urinalysis was normal. Electrolytes, creatinine, blood urea nitrogen, bilirubin, and alkaline phosphatase were all normal. The cholesterol was 136 mg per 100 ml. The initial true thyroxin ( $TT_4$ ) was 23.2 micrograms per 100 ml (normal range, 3.0 to 7.5 micrograms per 100 ml) with a triiodothyronine ( $T_3$ ) uptake of 52 percent (normal range, 25 to 35 percent). The urine pregnancy test was positive. Electrocardiogram showed a sinus tachycardia with frequent premature atrial contractions, ST segment elevation, and terminal r wave inversion in leads II, III, AVF, and  $V_2$  through  $V_6$ .

On admission to hospital, treatment was begun with propylthiouracil, 800 mg per day in divided doses. Phenobarbital and propranolol, 40 mg per day in divided doses, were also given. Since the patient slept with the eyelids open, eye shields were provided for the exposure keratitis.

As thyroid function decreased, the dose of propylthiouracil was decreased. Rapid control of the premature atrial contractions allowed the discontinuation of the propranolol. There was, however, no clinical decrease in size of the thyroid or disappearance of the bruit and thrill during the stay in hospital.

At the time of leaving hospital the  $TT_4$  was 11.2 micrograms per 100 ml and the  $T_3$  uptake was 36 percent. Medications included propylthiouracil, 100 mg three times daily, and phenobarbital, 15 mg three times daily. Our plan was to recommend subtotal thyroidectomy in the middle trimester of pregnancy.

DR. SMITH: Thank you very much, Dr. Fitzgerald. We would like to call on Dr. Francis Greenspan to discuss this patient and this particular problem. I would like to ask Dr. Greenspan, is there an increased incidence of Graves' disease during pregnancy? What are the problems which occur in the diagnosis of hyperthyroidism in the presence of endocrine abnormalities of pregnancy? How do these abnormalities alter one's therapeutic approach?

DR. GREENSPAN:\* Thyrotoxicosis and pregnancy are a relatively rare combination. At the University of California San Francisco from 1964 to 1968, we had approximately 10,000 deliveries and only eight pregnancies accompanied by thyro-

toxicosis, an incidence of about 0.08 percent. Becker and Sudduth<sup>1</sup> found 30 patients with thyrotoxicosis in a review of about 150,000 pregnancies, an incidence of 0.02 percent. In their review of the literature (until 1959) they reported that the incidence ranged from 0.02 to 3.7 percent and averaged about 0.2 percent. The important point is that this is a relatively rare combination. The reason it is rare is that patients with thyrotoxicosis are usually relatively infertile. The two most common clinical situations are (1) thyrotoxicosis may antedate pregnancy, be brought under control with medication, and then pregnancy occur in a partially treated patient and (2) thyrotoxicosis may develop after the onset of a normal pregnancy. The patient under discussion, however, became pregnant very early in the course of the thyrotoxicosis, so that both developed almost simultaneously.

### Diagnosis of Thyrotoxicosis During Pregnancy

*Clinical Findings:* The recognition of thyrotoxicosis during pregnancy may be very difficult. The normal pregnant patient may complain of excessive warmth and nervousness. She may have signs of tachycardia, tremor, and some slight thyroid enlargement. The clinical signs that suggest thyrotoxicosis are the presence of eye signs, such as lid lag, lid retraction, stare, and exophthalmos. A bruit heard over the thyroid gland is very suggestive. Finally, the occurrence of weight loss despite a good appetite is a characteristic clinical sign. Many patients lose weight early in the pregnancy because of "morning sickness," but this weight loss is obviously associated with poor appetite. When a patient either loses weight or fails to gain weight despite a good caloric intake, one must suspect the presence of thyrotoxicosis.

*Laboratory Tests:* The diagnosis of thyrotoxicosis in pregnancy can easily be made on the basis of commonly available laboratory studies, but it is important to recognize that many of these tests have a different range for the normal pregnant female than for the nonpregnant female. A summary of the tests of thyroid function in pregnancy is presented in Table 1.

In 1951, Dr. Evelyn Man<sup>2</sup> presented data on the serum precipitable iodine in the course of normal pregnancy. She showed a striking rise in the serum precipitable iodine or the protein-bound iodine (PBI) occurring about the fourth week in

\*Francis S. Greenspan, M.D., Clinical Professor of Medicine.

TABLE 1.—Tests of  
Thyroid Function in  
Women

Test	Normal Nonpregnant	Normal Pregnant	Hyperthyroid Pregnant
Protein-Bound Iodine (micrograms per 100 ml).....	4.0 to 8.0	6.0 to 12.0	>12.0
True Thyroxin (TT <sub>4</sub> ) (micrograms per 100 ml).....	3.0 to 7.5	5.5 to 10.5	>10.5
Resin Triiodothyronine Uptake (RT <sub>3</sub> ) (percent) .....	25.0 to 35.0	<21.0	>25.0
Free Thyroxin Index (product of TT <sub>4</sub> multiplied by RT <sub>3</sub> ).....	0.75 to 2.6	0.75 to 2.6	> 2.6
Free Thyroxin (nanograms per 100 ml)	4.5 to 8.5	3.2 to 5.6	> 8.5

pregnancy. The PBI remained elevated throughout the duration of the pregnancy, dropping back to the normal range about a month after delivery. Initially, it was suspected that there might be some thyroid dysfunction in pregnancy, although it was clear there were no other signs of thyrotoxicosis. With the discovery of thyroxin-binding globulin and the recognition of its importance in the transport of thyroxin, the PBI changes in pregnancy were clarified.

Robbins and Rall<sup>3</sup> in 1957 discovered in normal pregnant females the increased capacity of the serum to bind thyroxin and showed that this capacity rose early in pregnancy, remained high throughout pregnancy, and returned to normal about one or two months after delivery. It is the rise in thyroxin-binding globulin in pregnancy which is responsible for the elevated PBI. More recently, we have measured TT<sub>4</sub>, as determined by the method of Pattee and Murphy,<sup>4</sup> which has the advantage that it is not interfered with by inorganic or organic iodides. The normal range for TT<sub>4</sub> in the nonpregnant female is 3.0 to 7.5 micrograms per 100 ml and in the pregnant female 5.5 to 10.5 micrograms per 100 ml.

The resin T<sub>3</sub> uptake, another commonly available thyroid function test, measures the degree of saturation of thyroxin-binding protein. In normal persons, the resin uptake is 25 to 35 percent. In the pregnant woman, the elevated level of circulating thyroxin-binding protein results in more available binding sites in the serum, so that the spillover onto the resin of the added T<sub>3</sub> is diminished; therefore, the T<sub>3</sub> uptake is depressed. The normal T<sub>3</sub> uptake in pregnancy is usually below 21 percent. The characteristic findings in pregnancy, then, are a high PBI, a high TT<sub>4</sub>, and a low T<sub>3</sub> uptake.<sup>5</sup>

We have used the product of PBI multiplied by T<sub>3</sub> uptake, or TT<sub>4</sub> multiplied by T<sub>3</sub> uptake, to give us an index of free thyroxin (Chart 1). In pregnancy, the TT<sub>4</sub> is elevated, the T<sub>3</sub> uptake is depressed, but the product of the two still results in

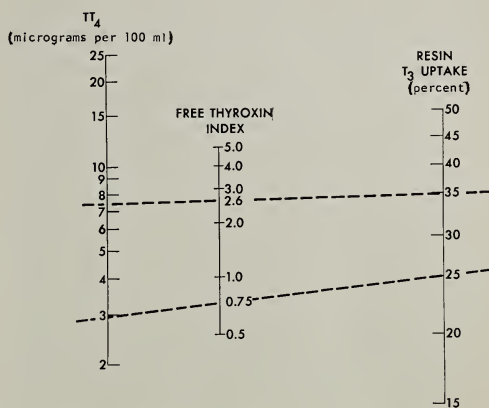


Chart 1.—Nomogram for free thyroxin index. The product of the true thyroxin iodide (TT<sub>4</sub>, microgram per 100 ml) and the resin T<sub>3</sub> uptake (percent) yields the "free thyroxin index" in arbitrary units. The dotted lines indicate the range of normal values.

a normal free thyroxin index. The use of a nomogram such as Chart 1 makes this calculation quite simple. Actual measurements of free thyroxin in pregnancy reveal it to be in the same range as for the nonpregnant woman.<sup>6</sup>

The diagnosis, then, of thyrotoxicosis in pregnancy is simply that there is a higher level of circulating thyroxin in the thyrotoxic pregnant woman than there is in the nonthyrotoxic pregnant woman. Therefore, in the patient with hyperthyroidism and pregnancy, the PBI is usually over 12, the TT<sub>4</sub> is over 10, and the T<sub>3</sub> uptake is usually over 25 percent (Table 1). In the patient presented today, the TT<sub>4</sub> was 23 micrograms per 100 ml, and the T<sub>3</sub> uptake was 52 percent. These values yield a free thyroxin index of about 12, which is enormously elevated.

## Placental Transport

**Iodide:** In dealing with pregnant patients with thyrotoxicosis, we must consider the problem of



placental transport in order to evaluate the effect of the disease and proper treatment on the fetus. The placenta is considered to be freely permeable by iodide ion, but there has been a question as to when the fetal thyroid begins to function and take up iodine. This has been studied by Evans and his colleagues,<sup>7</sup> who administered radioiodine to women who were about to have a therapeutic abortion. He was able to demonstrate that the fetal thyroid began to accumulate iodine shortly after the third month of the pregnancy. This was indirectly confirmed by Russel and coworkers,<sup>8</sup> who reported two patients with thyroid cancer treated inadvertently with radioiodine at about three months of pregnancy. In both instances, the neonate was found to be decidedly hypothyroid. Although these patients received very large doses of radioiodine (75 to 225 millicuries), in general we wish to avoid the use of radioiodine after the third month of pregnancy because of the possibility of radiation damage to the fetal thyroid. Large doses of inorganic iodide have been shown to induce goiter and hypothyroidism in the fetus. In the case reported by Galina and coworkers,<sup>9</sup> the doses of iodide were extremely large (about 1,200 mg per day) and the infant actually died of asphyxiation from a large iodide-induced goiter. This must be an extremely rare situation, but it indicates caution in the use of large doses of iodides during pregnancy, as well as avoidance of radioiodine during pregnancy.

**Propylthiouracil:** Early studies on propylthiouracil in animals demonstrated that it crossed the placenta very easily and produced hypothyroidism and goiter in the pups.<sup>10</sup> In 1957, Krementz and coworkers<sup>11</sup> reported 15 infants with goiter from mothers treated with propylthiouracil during pregnancy. Although this would seem to contraindicate the use of propylthiouracil during pregnancy, the incidence of goiter in the fetus may depend directly upon the dose of propylthiouracil administered to the mother, so that a safe dose of propylthiouracil can be achieved, as I will discuss later.

**Thyroxin:** The transport of thyroxin across the placenta at term was studied by Grumbach and Werner<sup>12</sup> in 1956. They administered radioiodine labeled thyroxin to the mother shortly before delivery, blocked the gland with iodide, and then measured the maternal-fetal ratio of labeled thyroxin from appropriate blood samples. They found that the maternal-fetal blood ratio was approximately 10:1 at 7 hours, and 7:1 at 16 hours after

injection, suggesting a very slow transfer of thyroxin across the placenta.

Fisher and coworkers,<sup>13</sup> using a slightly different technique, actually calculated the rate of transport of thyroxin across the placenta. They showed that with a dose of 2 to 4 mg administered to the mother, the transport rate was roughly 4 micrograms of  $T_4$  per hour, and with 8 mg administered to the mother, the placental transport rate was 14 micrograms per hour. These transport rates are extremely slow.

Why does thyroxin cross the placenta so slowly? French and Van Wyk<sup>14</sup> suggested that this rate primarily results from the tremendous thyroxin binding capacity of maternal serum in relation to fetal serum.

The practical problem of how to get enough thyroxin into the mother to raise the fetal serum thyroxin level was approached by Carr and his colleagues<sup>15</sup> in 1959. They administered 20 to 24 grains of desiccated thyroid daily to two mothers who had previously borne athyreotic children. This is a very large dose, about ten times the normal adult requirement of desiccated thyroid. With this large dose, however, they were able to demonstrate normal development in one child who was later shown to be athyreotic. The important point about this study is that in order to achieve normal serum thyroxin levels in the fetus, one must administer very large doses of thyroxin or thyroid hormone to the mother.  $T_3$  also crosses the placenta quite slowly, so that there is no real advantage to treating mothers with this material in an effort to achieve euthyroidism in an athyreotic fetus.<sup>16</sup>

#### TSH and LATS

Anterior pituitary thyrotropic hormone (TSH) does not cross the placenta. The long-acting thyroid stimulator (LATS), an immune gamma globulin, crosses the placenta very well. Indeed, the active placental transport of LATS is probably the cause of neonatal Graves' disease. In this syndrome, the mother is or was hyperthyroid and usually has exophthalmos or recurrent Graves' disease. The child is born with periorbital edema, slight exophthalmos, goiter, tachycardia, fever, and a very skinny appearance; and the  $TT_4$  and  $T_3$  uptakes are decidedly elevated. Treatment usually involves supportive therapy with food and fluids, plus the administration of iodides and propylthiouracil. The child spontaneously recovers in about



TABLE 2.—*Management of Thyrotoxicosis in Pregnancy*

<i>Treatment</i>	<i>Pregnancies (number)</i>	<i>Maternal Mortality (percent)</i>	<i>Fetal Mortality (percent)</i>	<i>Fetal Abnormalities (number)</i>	<i>Reference</i>
Supportive .....	31	0	45	0	18
Potassium iodide, surgery .....	41	0	4	0	19
Propylthiouracil, iodide, surgery ..	21	0	24	0	20
Mercaptoimidazole, iodide, surgery, with or without T <sub>4</sub> postoperatively .....	21	0	5	0	20
Propylthiouracil, iodide, surgery ..	38	0	5	0	21
Propylthiouracil .....	19	0	0	0	22
Propyl- or methylthiouracil or mercaptoimidazole, terminated antepartum .....	16	0	31	1	23
Propylthiouracil, T <sub>4</sub> .....	27	0	7.5	1	24
Propylthiouracil, T <sub>4</sub> .....	32	0	9	0	25

a month, usually with no residua. McKenzie<sup>17</sup> has shown high levels of LATS in both mother and child, with a gradual disappearance of the LATS level in the infant. The half-life of LATS is about one or two weeks. These observations are a strong argument in favor of the concept that LATS, or an antibody similar to it, is actually an etiological factor in the development of Graves' disease.

In summary, then, we recognize that iodide and propylthiouracil cross the placenta very easily, thyroxin and T<sub>3</sub> cross very slowly and against a gradient, and TSH does not cross the placenta at all. LATS, like other small antibodies, is transported across the placenta quite well and may actually cause disease in the infant.

## Management

A series of reports concerning the management of thyrotoxicosis in pregnancy is summarized in Table 2. In 1929, Gardiner-Hill<sup>18</sup> reported a group of patients who were pregnant and thyrotoxic and who were carried through pregnancy with only supportive therapy. The maternal mortality was zero, but the fetal mortality was 45 percent (including abortions, stillbirths, and premature infants who died very shortly after birth). Mussey and Plummer<sup>19</sup> in 1931 reported a group of 41 patients who were treated with potassium iodide and surgical operation, and fetal mortality was only 4 percent. In 1960, Bell and Hall<sup>20</sup> reported a group of patients who were treated with propylthiouracil and iodide, and then subtotal thyroidectomy. The fetal mortality was somewhat higher, about 24 percent. He noted that many of these patients became hypothyroid postoperatively. Therefore, he treated the next group of patients with thyroxin postoperatively and found that the fetal mortality dropped considerably. A later study with comparable therapy again revealed a fetal mortality of about 5 percent.<sup>21</sup> These data indicate that operation pre-

ceded by propylthiouracil therapy and including postoperative thyroxin treatment to the mother is a very satisfactory way of handling this problem.

On the other hand, the use of propylthiouracil alone is also quite satisfactory. Therapy of this type was first reported by Astwood<sup>22</sup> in 1951. He treated 19 patients with no incidence of fetal or maternal mortality. He used propylthiouracil in initial doses of around 300 mg and reduced the dose as the disease improved. Later workers were not quite so careful. Piper<sup>23</sup> in 1954 treated patients with methyl- or propylthiouracil in doses of 400 to 500 mg daily. He stopped the medication two months before delivery. With this procedure, fetal mortality was about 31 percent. Asper<sup>24</sup> and Herbst<sup>25</sup> used propylthiouracil in addition to thyroxin. They administered 300 mg of propylthiouracil initially, then reduced the dose and added thyroxin in doses of 0.2 to 0.4 mg daily. Their overall fetal mortality was 7.5 to 9 percent. As I have already pointed out, thyroxin does not cross the placenta in significant quantities, and since the goal in therapy is to reduce the dose of propylthiouracil to the minimum required to maintain the mother euthyroid, the addition of thyroxin is really quite unnecessary. If the patient can be controlled on doses of 300 mg or propylthiouracil (in divided doses) initially, with maintenance doses of 100 to 150 mg daily, the likelihood of fetal hypothyroidism is extremely small.

In summary, we have two good methods for the management of thyrotoxicosis in pregnancy. The first is preparation with propylthiouracil and iodide and subtotal thyroidectomy in the middle trimester of pregnancy. This regimen is associated with a very low maternal mortality and, provided the patient receives supplemental thyroxin during the latter part of pregnancy, the fetal mortality is also very low. As a second method the patient can be treated with propylthiouracil alone, keeping

the dosage down to the minimum which will keep the mother euthyroid.

In the particular patient under discussion today, the decision was made to prepare her for subtotal thyroidectomy in the middle trimester of pregnancy. I think this will be a very effective and satisfactory form of therapy.

DR. SMITH: Thank you very much, Dr. Greenspan. Are there any questions or comments?

DR. HAVEL:\* Will you comment on fetal abnormalities when propylthiouracil is given at the time of conception?

DR. GREENSPAN: I do not think there are any data. There are reports of a fairly large number of patients who became pregnant while taking propylthiouracil. They were euthyroid and were carried through the pregnancy on small doses of the drug without evidence of fetal abnormality. The major problem one gets into is abortion, uncontrolled disease, or goiter in the child if the dosage of propylthiouracil is too high for too long. We have not really seen evidence of other congenital malformations in newborns when the mothers were treated with relatively low doses of propylthiouracil throughout pregnancy.

QUESTION: Would propranolol alone be useful in management of thyrotoxicosis in pregnancy?

DR. GREENSPAN: I have had no experience with propranolol used alone. We have in general felt that it was extremely important to bring the level of circulating thyroxine down by appropriate antithyroid drugs. Propranolol has been used very effectively in management of thyrotoxic storms,


which may occur in a patient who is untreated and goes through labor, but I have had no experience with its use alone.

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\*Richard J. Havel, M.D., Associate Director, Cardiovascular Research Institute, and Professor of Medicine.

# RELEVANCE



## today and tomorrow

## in Medical Education

### A FORUM WITH A PURPOSE

*Students of today question the relevance of much of their formal education. In medical schools the concern is particularly with the relevance of the educational experience to the professional commitment in modern society. To engender discussion of the subject, CALIFORNIA MEDICINE in its January issue printed eight essays by authors known to have keen interest in the subject.*

*Readers in California and elsewhere are invited to take part in a continuation of the forum in succeeding issues. The following are contributions selected from those received to date. Others will be published in the months ahead. At an appropriate time the material will be collated and, if feasible, the distillate will be prepared in the form of a statement.*

*If you have thoughts on the subject, just address them to the editors of CALIFORNIA MEDICINE, 693 Sutter Street, San Francisco, California, 94102. Keep your essays short, please.*

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FOLLOWING ARE THE objectives of the School of Medicine of the University of California in San Francisco.

I. *To have the student acquire the basic knowledge and skills necessary for his profession by:*

a. Learning normal development, structure and function from the molecular level to the complex psycho-social factors affecting individuals in a society.

b. Understanding how genetic, physical, chemical, biological, psychological and sociological factors interact to cause abnormal development, structure and function.

c. Learning the major sources of medical information, how to use them, and how to record, store and retrieve his own data.

d. Studying the natural history of disease and the ways of promoting health and preventing disease.

e. Understanding and using appropriate diagnostic, therapeutic and preventive methods with knowledge of their limitations and consequences; emphasis will be placed on common diseases and on emergencies threatening life. The specific topics would include:

1. Obtaining information from patients and other sources;
2. Performing adequate physical examinations and certain basic laboratory tests;
3. Interpreting diagnostic data and initiating therapy;
4. Conveying conclusions in coherent, practical terms to the patient and his family;

5. Evaluating the success of medical management;

6. Integrating the medical and social services necessary for patient management, with particular reference to the interaction between the patient's illness and his environment and on planning for long term care.

f. Understanding how to work with other professionals and nonprofessionals, hospitals, community organizations and State and Federal agencies in providing optimal medical care.

g. Understanding the development of attitudes in the care of the sick and of ethical standards in medical practice with emphasis on ethical and socio-economic problems of patient care and medical research.

II. *To encourage certain fundamental attitudes:*

a. Respect and compassion for the individual.

b. Understanding his own attitude toward people, and his own emotions when treating patients.

c. Intellectual honesty, including recognition of his personal limitations, and the need to supplement his own ability with the skill and knowledge of others.

d. Appreciating scholarship and the importance of research.

e. Appreciating that learning in the health sciences is lifelong and that continual education and revision of concepts, knowledge and skills are essential.

III. *To develop a physician-scientist who has both the ability for self-education and an understanding of his goals by:*

a. Learning the scientific method and its use in solving biological and medical problems and in critically reviewing the literature.



b. Exposure to various disciplines and specialties to permit students to make rational career choices.

c. Intensive study of selected aspects of human biology and medical practice so that the student:

1. Will gain above average knowledge, skill and understanding of those aspects in which he has special interests;
2. Will acquire confidence and an increased ability to function independently and to assume professional responsibility in those areas.

The foregoing objectives were developed through the cooperation of students and faculty in preparation for an extensive revision of the curriculum. This revised curriculum is now in its first or transitional year of operation. Those of you who weigh each of these objectives rather than scan the list will note that there is an effort to broaden the educational goals to include elements that in the past were not considered relevant to medical education. In an articulate and thoughtful article by Mr. Stalcup, a student of medicine in our school, which appeared in the initial series of this Forum, he stated "that much of what passes for medical education these days is irrelevant." Knowing Mr. Stalcup, I would guess that he makes this statement for justifiable provocative reasons. Having been exposed to some of this in recent years, and being emotionally distressed at the technics of confrontation and demands, I still must admit that there does seem to be some need for provocation, at least, if reasonably prompt beneficial change is to be effected.

If one accepts the fact that there are sick people in the world of today and that these people need to be treated, "much of what passes today for medical education" is relevant. Undoubtedly much trivia and detail have been included but it is still relevant if we are to cure the sick. To me, what needs to be done is to rid the curriculum of trivia and details and devote that time to things of relevance in medical education that have been heretofore neglected. Overpopulation (with its attendant potential for famine), environmental pollution, poverty and many other ecological factors are examples of items that are relevant to contemporary medical education.

I endorse Mr. Stalcup's idea that one of the more significant factors of relevance in medical education is a reorientation of education in medicine to emphasize the effort to maintain a state of health rather than treat sickness. I believe we differ somewhat on the relative emphasis on these needs in the practice of medicine. Unless I misinterpret what he says, he relegates the traditional treatment of the sick to those physicians who have "to manage those who are essentially treatment failures of the health specialists." Until we reach that happy millenium when all of us, in or out of medicine, have conquered the overwhelming ecological problems relating to disease, there is an urgent and tremendous need for treating the sick and, as a result, continuing to include this as a relevant, but not sole, element of medical education. Certainly, there is something that can be done to prevent the cirrhosis due to alcoholism, the lead poisoning of poor housing and the toxic effects of pesticides. However, because of my traditional background, I find it difficult to maintain the state of well-being in the woman who is unaware that she is developing a malignant tumor of the ovary until there is a palpable mass or the man who is unaware that he has encroachment upon functioning coronary vessels until he has an incapacitating or fatal occlusion. I think there are going to be many patients, for quite a while, with ovarian tumors and inadequate coronary vessels, perhaps more than those with lead poisoning.

Until we discover how to prevent ovarian tumors and coronary insufficiency, I think there is an urgent relevance to that part of medical education that teaches potential physicians how to treat the sick.

Finally, as has been pointed out by others speaking in this Forum, another factor introducing more relevance into medical education is instruction and experimentation in the systems of delivery of health care. The schools of medicine have done a notoriously poor job of education of the physician of yesterday and today in the complicated process of delivery of health care. Whether or not the current system is adequate or appropriate (and there is disturbing evidence that it is neither adequate or appropriate) there is urgent need to involve the schools of medicine, their students and faculty, in efforts to test the system and improve where needed.

My plea then is for the enthusiast not to assume that current medical education is irrelevant but rather to work towards introducing more items of relevance. I doubt that we need to relegate our current breed of cat to extinction but to develop additional breeds of cat such as the "urban health specialist," the "ghetto medicine specialist," the "population and nutrition specialists" and the "environmental hazard specialists." Just think of all the nice new societies and journals we can have.

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IN PRAGMATIC TERMS, a relevant medical education is one that is useful. In this era of an increasingly compact world neighborhood, population pressure seems to force increased neighborliness as a price for survival. The medical profession, in particular, faces increasing international challenges. An unprecedented interest in international service among medical students indicates that here too the student generation is ahead of us in their understanding of what is relevant for the world of tomorrow.

The greater availability of elective time in medical schools permits interesting overseas assignments. Such activities went through some initial erratic phases. Most programs have now stabilized so that students can choose fairly structured situations where they will have both psychologic and professional support. An important development has been that as a result of stimulation from the Association of American Medical Colleges each medical faculty has appointed a liaison officer for international activities. During the past year the Division of International Medical Education of the AAMC did a survey of medical school involvement in international work which included site visits to 51 campuses. Thirty-eight of these 51 medical schools give elective credit for international experience and have diverse arrangements and affiliations with foreign institutions both in teaching and research. In some schools they have international clubs to study work overseas, with the group at Buffalo having been particularly active for a number of years. The SAMA has recently been participating with increas-

ing enthusiasm in the work of the International Federation of Medical Students and through this mechanism developing its own student exchange program. These and many other student activities show clearly that sizable numbers of medical students consider international experience to be a relevant component of medical education.

The most obvious usefulness of international experience to the medical student is stimulation and preparation for those who are considering either long or short term careers overseas. The growing concern of this idealistic student generation in the welfare of the needy people of the world is clearly going to stimulate more doctors into looking for foreign service opportunities. There will probably be an expansion of work under international agencies such as WHO. And in spite of the present attitudes in Congress it is inconceivable that the U.S. will not continue some sort of technical assistance in developing countries. The U.S. has now fallen behind several European countries in our rate of giving. At present, the major thrust of assistance is in family planning and nutrition. It is increasingly evident, however, that to get acceptance of family planning in developing countries, it is almost essential to integrate these services with maternal and child health programs.

Many individuals who have been exposed to international work as part of their medical education will work in the United States. The most relevant effect of this experience is the tremendous change in values and attitudes that occurs in doctors who have experienced the problems in developing countries. Almost uniformly they come back from overseas work changed men and women, seeing all sorts of situations and relationships which were totally outside of their perception before. The stark reality of massive human need increases awareness of social factors. Looking at health problems in a different culture provides an objectivity which could never be achieved in the home environment. In the doctor's own environment, social conditions are accepted just because that is the way they have always been and it is hard to see the possibilities of change. In a dramatically different cultural situation, interactions and incongruities between ecological conditions are more evident. Having seen these realities in an international setting, the young doctor is better prepared to observe with greater objectivity in his own culture.

Another major contribution is being made to our own health services from international contacts. Although we have long prided ourselves on the research contributions that America's massive development of science has given the world, it is now becoming evident that in some important research areas other countries are way ahead of us. This applies particularly to health services research, population studies, comprehensive health planning and experimental approaches to the development of manpower. These have now been designated the highest priority research subjects by our own granting agencies in Washington and private foundations. Much of what we know now has been learned overseas. Many of the American leaders in these critically important areas received their basic experience in international programs. In order to become relevant to modern social needs American medical education has to catch up with many of the developments that have occurred in medical schools overseas.

The Biblical principle of "bread cast upon waters" is now proving true for us in that many of these innovations in foreign countries were directly stimulated by Americans working for foundations, missions or official agencies. To offset the shame that we feel, or should feel, from the growing "brain drain" of doctors from countries where they are needed far more than here we need to participate more actively than ever in international work. Last year half of all doctors entering medical service in the U.S. were graduates of foreign medical schools.

The basic truth underlying all of our previous experience is that the greatest good will come from a synergistic development of medical education at home and abroad.

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THE EIGHT ESSAYS that have appeared thus far share a common framework in addition to their being part of a forum on "Relevance for Today and Tomorrow in Medical Education." They all start with education and then move toward a discussion of the social aspects of health care delivery. Are they not saying that before medical education can be truly relevant, its goals, even though very broad, must be accurately defined—and accepted?

If we assume that the role of medical education is to prepare its graduates to care for the sick, that is one thing. If they are to maintain the health of the people, that is another. If they are to enhance knowledge of the processes of disease of whatever origin, that is still a third. By comparison the first is essentially technical, the second sociological and the third scientific. All of these educational goals are relevant to the needs of society, but the amount of time and effort devoted to each of them in the educational process may be out of proper balance. This impression is distilled from reading the forum articles and from a consideration of the problems in health care delivery faced today by medicine and allied professions.

Voices from every direction are saying that the medical care delivery system in the United States today is in "crisis" owing to inadequate access for many, fragmentation of care, shortage of manpower, stress on therapy rather than prevention, and other shortcomings. At the same time, there exists a polarization within the profession itself. At opposite extremes stand the two major professional archetypes; on one end, the community physician, buttressed by fee for service and the personal doctor-patient relationship; on the other, the academic physician, guided by his expanding bibliography and his conviction that research is inseparable from education. The Federal Government has encouraged this dichotomy by providing billions for fees through Medicare and Medicaid to the first group, and a lesser but highly significant amount for biomedical research to the other. Fortunately, most physicians stand somewhere between these extremes. Nevertheless, as a result of these and other intraprofessional differences, plus the increasing demand by the community for an improved health care delivery system, a growing number of medical students are raising the cry that medical schools lack relevance.

Is it possible that our splintered profession can once again approach unity by acting as one group to stabilize and renovate the health care delivery structure, so that it will meet not only the demands but the actual health needs of the nation? Is it possible the Federal Government might encourage this by diverting some funds for the study and development of such a system? If the answer to both questions could be "yes," the subject of relevance of medical education would gradually become old hat because its goals would once again become straightforward, clearly manifest, and widely accepted.



# Important Advances in Clinical Medicine

## *Epitomes of Progress-- Surgery*

*The Scientific Board of the California Medical Association presents the following inventory of items of progress in Surgery. Each item, in the judgment of a panel of knowledgeable physicians, has recently become reasonably firmly established, both as to scientific fact and important clinical significance. The items are presented in simple epitome and an authoritative reference, both to the item itself and to the subject as a whole is generally given for those who may be unfamiliar with a particular item. The purpose is to assist the busy practitioner, student, research worker or scholar to stay abreast of these items of progress in Surgery which have recently achieved a substantial degree of authoritative acceptance, whether in his own field of special interest or another.*

*The items of progress listed below were selected by the Advisory Panel to the Section on Surgery of the California Medical Association and the summaries were prepared under its direction.*

Reprint requests to: Division of Scientific and Educational Activities, 693 Sutter Street, San Francisco, Ca. 94102

### Cardiopulmonary Resuscitation

Cardiopulmonary resuscitation (CPR) has been shown to maintain adequate ventilation and circulation since its introduction to clinical medicine in 1960 by Kouwenhoven, Jude, and Knickerbocker. Adequate ventilation may consist of mouth to mouth resuscitation only, may require the use of a bag and mask device, or may necessitate the insertion of an endotracheal tube combined with a positive pressure ventilator. Circulatory support is usually provided by external cardiac compression. Rhythmical coordination of ventilation and external cardiac compression has been shown to provide optimal resuscitation. (External compression rate of 60 per minute with ventilatory rate of 12 per minute or ventilation performed after every fifth compression.) Rapid treatment of the precipitating cause of the cardiac arrest may require the intracardiac injection of drugs and the

use of electrical defibrillation. Of equal importance is the treatment of shock and the correction of metabolic acidosis and electrolyte disturbances.

Future developments in CPR include the use of assisted circulation in selected patients and has been reported as an "extended concept" of CPR. Kennedy showed that although the proportion of long-term survivors is small there are some patients who cannot be salvaged by the conventional CPR measures and have been resuscitated with the addition of partial cardiopulmonary bypass techniques.

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Kennedy JH: Assisted circulation: an extended concept of cardiopulmonary resuscitation. *J Thorac Cardiovasc Surg* 57:3, 1969



## Antilymphocyte Globulin (ALG) in Clinical Organ Transplantation

Antilymphocyte globulin (ALG) prepared from horses immunized against human lymphocytes is being widely employed for its immunosuppressive action in recipients of vital organ transplants. The cells used in immunization have been derived from spleen, thymus, lymph nodes, thoracic duct or blast cells produced in vitro. Variation in the source of cells used for immunization of horses and the method of refining ALG may result in a variable product.

Immunosuppressive action may not parallel a rising cytotoxicity titer. The most widely employed test of immunosuppressive effect has been a biological test in primate skin grafts developed by Balner.

The potent effect of ALG on cellular immunity may expose the recipient to an increased risk of infection by opportunistic fungi, protozoa. There may be an increased risk of malignant disease in the graft recipient receiving ALG.

The optimum method for production and utilization is yet to be elaborated.

DONALD C. MARTIN, M.D.

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## Circulating Antibodies in Renal Transplant Recipients

Accelerated rejection of renal allografts frequently correlates with the presence of pretransplantation antibody in recipients. These antibodies may occur as a result of previous pregnancy, whole blood transfusion or tissue grafts. If such antibodies are active against donor antigens there is an 80 percent chance of immediate graft failure. This apparent humoral response has histologic features distinctly different from the classical

cellular, delayed graft rejection. All potential organ graft recipients should be tested for the presence of preformed circulating antibodies. This is done by testing recipients' serum against cells from a large number of random persons. Those with positive reactions should be tested with donor cells before organ transplantation to avoid the accelerated rejection.

DONALD C. MARTIN, M.D.

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## Cadaver Organ Sharing

To achieve the maximum utilization of kidneys from cadaveric sources and to employ matching of donor recipient pairs by serological testing of leukocyte antigens a large number of transplantation centers are embarking upon a collaborative program. This is an extension of programs initiated in the large metropolitan areas of Los Angeles and New York. Kidneys have been transported by air between California and Louisiana, Utah and Oklahoma, California and Utah.

Although histocompatibility testing in cadaveric renal transplantation has not been proved as efficacious as in family donor transplants, it is hoped that all available kidneys and other vital organs will be utilized by such a cooperative program.

All prospective recipients are tissue typed and kept on file in the laboratory of Dr. Paul Terasaki at U.C.L.A. Prospective donors are usually typed antemortum, at which time the two most compatible kidney recipients are selected. The donor and recipient teams decide upon the acceptability of the organs and the method of transportation.

DONALD C. MARTIN, M.D.

### REFERENCE

- Patel R, Glasscock R, Terasaki PI: Serotyping for homotransplantation. XIX. Experience with an interhospital scheme of cadaver kidney sharing. *JAMA* 207:1319, 1969

## Renal Transplantation Results

Most of the clinical renal transplants performed in this country are reported to a national registry in Boston. The registry compiles data on the individual patients and publishes an annual report. The estimated one-year functional survival of transplanted kidneys from various donor sources is as follows:

Donor	Percent	Standard Error
Monozygotic Twins	91	4
Sibling	91	3
Parent	83	4
Other blood relative	67	7
Cadaver	42	5
Unrelated living	58	20

It is apparent the results of clinical renal transplantation surpass many surgical procedures for other forms of life threatening disease.

DONALD C. MARTIN, M.D.

### REFERENCE

Askman CFC, Atkinson JC, Barnes BA, et al: Sixth report of the human kidney transplant registry. *Transplantation* 6:944, 1968

or sensitized lymphocytes have also been shown to possess antibodies inhibiting the growth of chemically induced tumors.

The virally induced tumors apparently result in incorporation of the virus into genome of the host cell. The chemically induced tumor apparently results from an alteration in the DNA in the specific cell of a given host. Perhaps the most exciting development in the entire field comes from the recent work on cell hybridization in which it has been demonstrated that it is possible to fuse a normal cell with a neoplastic cell and thereby alter the antigenicity of the neoplastic cell so that it no longer grows in a susceptible host. This would imply that the genes for normality are dominant over the genes for cancer and that the weak antigens on the surface of the cancer cell can be converted to strong incompatible antigens which no longer are permissible for transplantation in suitable recipients. The techniques for cell hybridization must be exploited more fully, first in the experimental laboratory, and we may hope in man over the next few years if progress is to be made in cancer immunology at the clinical level.

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### REFERENCES

Review of the National Symposium on the Immunology of Cancer. *Cancer Res* Dec 1969

Richards V: Immunology of Cancer. *Amer J Surg* 118:498-506, 1969

## Cancer Immunology

During the past 20 years, the immunology of experimental cancer has been extensively investigated. The cancers of viral origin possess an antigen common to all the tumors induced by this virus regardless of the species of animal in which the tumor occurs. It is possible to produce antibodies against the virus and immunize animals against the induction of tumors by the virus.

The experimental tumors induced by chemical carcinogenesis have a specific change in the cancer tissue which can only be transmitted to inbred strains of identical animals. Immunity against these chemically induced tumors can also be demonstrated by excising portions of the tumor after it has started to grow and reinjecting tumor cells back into the identical animal, whereupon they commonly failed to grow. The injection of irradiated tumor cells also induces an active immunity against the subsequent implantation of viable tumor cells and sensitized or immunized spleen cells

## Surgical Management of Transposition Of the Great Vessels

Until a few years ago, transposition of the great vessels was not a correctable disease. Three recent developments have drastically changed the management and prognosis of infants with this condition. First is atrial septostomy introduced by Rashkind. This consists of the introduction of a balloon catheter through the foramen ovale into the left atrium. Deflation of the balloon during withdrawal of the catheter creates an atrial septal defect. This operation can be safely performed in infants under the age of six months and has replaced the Blalock-Hanlon operation as the palliative procedure of choice in this congenital

anomaly. The second advance is the total repair of the defect by the method of Mustard. The operation consists of the construction of an infracardiac baffle employing a piece of pericardium to re-route blood flow. The third advance has been miniaturization of cardiopulmonary bypass apparatus which permits the technical application of the Mustard procedure.

JOHN E. CONNOLLY, M.D.

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### Use of Aortic Homograft to Replace The Aortic or Mitral Valve

While mechanical ball valve prosthetic devices have gained wide acceptance as replacements for diseased aortic, mitral and tricuspid cardiac valves, early and late embolization continues to be a significant complication of valve replacement. This is in spite of routine anticoagulation with five years or longer follow-up now being available for human aortic homografts employed as a replacement for the aortic valve. Rejection or valve cusp fatigue with insufficiency have been minor problems while embolization has been virtually eliminated even though anticoagulants have not been employed. The homograft valve is obtained fresh from cadaver and either used immediately or preserved for later use. The valve is sewn to a simple metal frame before insertion into the recipient. The technique probably would be more widely used if problems of homograft availability and harvesting could be solved.

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### Saphenous Vein Bypass for Coronary Artery Occlusive Disease

Direct endarterectomy of coronary artery atherosclerotic disease has gained only limited acceptance because of the diffuse nature of the disease process. Based on wide experience with saphenous vein bypassing of long blocks of leg arteries, a similar technique has been applied to the coronary arteries. The great saphenous vein is removed from the leg and placed in a reversed position from the ascending aorta to patent areas of the distal left, right or circumflex coronary arteries. Selection of suitable candidates for such operations depends upon good preoperative selective coronary arteriography. Early results of an increasing number of such bypass procedures indicate good patency and clinical relief of symptoms. This technique promises to supersede the currently popular Vineberg internal mammary revascularization procedure.

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### Resection of Dyskinetic Ventricular Muscle or Ventricular Aneurysms

The most common occlusion of the coronary arterial tree occurs at the orifice of the left anterior descending coronary artery. If the patient survives, the anterior surface and apex of the left ventricle is often replaced by scar tissue or a ventricular aneurysm. Either entity commonly causes left ventricular failure, angina or cardiac arrhythmia. Resection of the scar or aneurysm in properly selected patients may provide dramatic improvement due to more normal left ventricular contraction. Selection of candidates for such operations depends on heart catheterization and left ventricular cineangiocardiograms. Aneurysms or scar tissue of the posterior surface of the left ven-



tricle may also impair ventricle function and require excision.

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### Radioimmunoassay of Gastrin

One of the most significant recent advances in gastric physiology and in the diagnosis of disorders of gastric secretion is the development of a highly specific radioimmunoassay of gastrin in plasma and other body fluids and tissues. The development of this important clinical and research tool follows closely on the heels of the monumental discovery of the structure of the hormone gastrin by Gregory and Tracy in 1964. The several available techniques involve the preparation of a gastrin antiserum in animals (rabbits or guinea pigs) and the use of  $^{125}\text{I}$ -labeled gastrin as a tracer in the analysis. Plasma gastrin concentrations as low as 5 micromicrograms per ml are detectable. It has been shown that peripheral plasma gastrin levels in man are elevated in conditions associated with end-organ failure (gastric parietal cell hypofunction), such as pernicious anemia and cancer of the stomach, and that gastrin levels increase with age. Furthermore, it has been repeatedly demonstrated that plasma gastrin levels are markedly elevated in the Zollinger-Ellison syndrome (10 to 100 times normal), so that measurement of gastrin in peripheral plasma has become the most reliable method of diagnosing the presence of a gastrin-secreting non-beta islet-cell tumor of the pancreas. Although plasma gastrin assays currently are being done in only a few centers, it is anticipated that this valuable procedure will be widely available in the not too distant future.

MARSHALL J. ORLOFF, M.D.

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### Advantages of Continuous Positive-Pressure Breathing In Surgical Patients

Recent investigations have shown that continuous positive-pressure breathing (CPPB) may have significant advantages over the conventional intermittent positive-pressure breathing (IPPB) in the treatment of pulmonary complications in surgical patients. Ashbaugh et al have reported that CPPB has proved considerably more effective than IPPB in the treatment of adult respiratory distress syndrome associated with a wide variety of illnesses and types of trauma. CPPB usually produced a decrease in the difference between the partial pressure of the inspired oxygen ( $\text{Pi}_{\text{O}_2}$ ) and the partial pressure of the arterial oxygen ( $\text{Pa}_{\text{O}_2}$ ). A consistent rise in the ( $\text{Pa}_{\text{O}_2}$ ) was also noted. A significant decrease in the mortality associated with adult respiratory distress syndrome was reported. It was postulated that the CPPB may prevent alveolar collapse and atelectasis and may also reduce interstitial edema and congestion.

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### Recurrence in Colon Carcinoma

Concern for adequacy of blood supply and prevention of suture line recurrence and peritoneal seeding are principal factors in preparation for anastomosis of the colon or rectum after resection for carcinoma.

One notes color, arterial pulsation, and arterial bleeding from divided bowel ends and extent of bleeding from cut marginal arteries.

Recurrence at the suture line is most frequently due to desquamated tumor cells. Ligation of the colon and marginal vessels at adequate distance above and below the tumor lessens the spread of cancer cells into adjacent segments.

Irrigation of distal and proximal bowel with sterile water or 1:1500 bichloride of mercury is apparently useful in lessening viability of desquamated cells and improving the recurrence rate.

SANFORD E. FELDMAN, M.D.

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### Newer Concepts in the Management of Shock

Parenteral sodium-containing solutions in addition to blood or 5 percent albumin solution for repletion of circulating blood volume and interstitial fluid deficits is fundamental in the treatment of hemorrhagic and traumatic shock. The over-enthusiastic use of excessively large volumes of lactated Ringer's solution has been tempered by laboratory experiments and increasing clinical evidence of the malefic results of such usage. This abuse was apparently based on a misinterpretation of Shires' work regarding the use of balanced salt solution in the treatment of shock and it is the consensus, at present, that balanced salt solutions should be used in modest amounts.

During the past year laboratory studies of metabolic and endocrine changes occurring in acute hemorrhagic shock have indicated changes in glucose and insulin metabolism similar to those occurring in diabetes, and suggest a possible role for insulin to influence favorably intermediary metabolism in shock. This awaits further laboratory studies. As yet, no clinical data are available to evaluate the use of insulin in the treatment of shock.

The use of glucagon intravenously in treatment of critically ill patients and patients with septic shock has been also recently reported. The initial report indicates that glucagon is a safe and effective agent in improving cardiac function in critically ill patients postoperatively and additionally appears to reverse abnormalities in oxygen consumption in septic shock. However, the role of

glucagon in the management of shock also must be evaluated by additional studies.

LEONARD ROSOFF, M.D.

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### Blood Supply to Stomach

Until celiac and mesenteric angiography confirmed that previously noted pronounced variations in arterial supply to the stomach and duodenum occur, these variations have not always been adequately considered by operating surgeons.

While anastomotic supply is rich in the fundus and body, there may be areas of potential ischemia along the lesser curvature and first portion of the duodenum which may make normal circulation hazardous.

SANFORD E. FELDMAN, M.D.

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### Emergency Portacaval Shunt For Bleeding Esophageal Varices

Bleeding from esophageal varices in patients with cirrhosis of the liver has been a highly lethal disorder. Extensive experience has shown that two-thirds to three-fourths of cirrhotic patients have failed to survive the first episode of varix hemorrhage. During the present century, none of a variety of therapeutic regimens has significantly influenced the high mortality rate. However, re-

cently it has been demonstrated that emergency portacaval shunt, performed at the time of bleeding without prolonged attempts at nonoperative therapy and preparation, has effectively controlled the bleeding and has resulted in a substantial increase in both immediate and long-term survival. In one study involving unselected patients, the five-year survival rate following emergency portacaval shunt was many times greater than the survival rate associated with emergency medical treatment followed by elective portacaval shunt. Moreover, it has been shown by several workers that patients with

cirrhosis of moderate severity tolerate emergency shunt as well as elective shunt. It appears that early and definitive operative control of varix hemorrhage provides the cirrhotic patient with the greatest chance of living.

MARSHALL J. ORLOFF, M.D.

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### Extending the Hand Of the Physician

BY NATURE, EDUCATION and experience, physicians are great individualists. The public often looks upon them and indeed accuses them of acting like generals—independent in thought and action, frequently authoritarian in attitude, ready and willing to accept great responsibility, and in a sense ordering those associated with them professionally as well as the patient to a specific line of thought and action. Yet what patient, lying ill and helpless, doesn't want his physician to exhibit these qualities of strength as he brings to the bedside or the consultation room the best in the science and art of medicine?

Gradually over the years some of these attitudes and responsibilities have been shared with others. First they were shared with the nurse because she brought to the bedside the feminine touch of warmth and kindness, and later because, as advances in medical science brought increasing knowledge, she became indispensable in extending the hand of the physician.

With the growing importance of laboratory science, biochemistry and radiology, soon technicians and then aides in these fields assumed such important functions that even though patient contact was often brief, minimal or perhaps lacking, the part they played became an essential one in aiding the patient and the physician and in ad-

vancing the practice of medicine. And so the story repeated itself for physical, occupational, speech and other therapists, for dietitians, for technicians in recording and monitoring, for medical secretaries, medical record librarians, social workers and others. In fact some authorities say that there are more than 250 categories of workers who play a specific role in health care and, as members of the health industry, take part in association with physicians in the diagnosis, treatment and prevention of disease and in rehabilitation. At the beginning of this century there was one allied health worker for each physician; today there are approximately 13. Projections for the future indicate there may be 17 to 20 or even more such workers for each physician by 1985 or 1990. Surely both in numbers and in skill and ability they have extended the hand of the physician.

Despite this rapid growth in variety and numbers, there has been an orderliness and a wide acceptance of this development by patients and physicians alike. It has led to increasing institutionalization and organization in the delivery of health care. The hospital and medical center have become increasingly important; the individual less important, be he physician, nurse, therapist, technician or patient. The demand for health care has exceeded the supply of health manpower and facilities, and indeed has outgrown financial capabilities. The demand for the increasing variety and numbers of health personnel has basically come from the medical and nursing professions and from hospitals and other health care institutions.

Now comes a new demand for a new category of health manpower—the "physician's assistant"<sup>1</sup>—designed specifically to alleviate the shortage of physicians. This demand does not come as it traditionally has from the medical profession

broadly or from health care institutions; it has come from segments of the medical profession—from specialty groups such as orthopedic surgeons, ophthalmologists, obstetricians and pediatricians. Further, it has been stimulated by some leading medical educators, by those who visualize a role for military medical and hospital corpsmen returning to civilian life, and by those in education at the community college level. To date this movement lacks uniformity and orderliness, educational standards vary, problems of licensing and certification lie ahead and the role of such physician's assistants in the practice of medicine is uncertain. Fortunately the total number educated thus far is miniscule but the pressure for more is great—pressure basically and with a few exceptions not from within the medical profession.

Almost nothing is known about how physician's assistants will be accepted by patients and physicians. But it is time to think about it. When the demand has come from a specialty, as it has from orthopedists through the American Academy of Orthopedic Surgeons for an orthopedic assistant, it seems quite likely that the relationship between the physician, the assistant and the patient will be good, for such auspices presage careful supervision of standards and quality of education, a close working relationship between the orthopedist and the assistant and a clear-cut responsibility on the part of the orthopedist.

Will a similar relationship with a physician's assistant be developed in the case of the general practitioner, the family physician and the internist? These professional groups have not sought such assistants. If educated in large numbers will *physician's assistants* be acceptable in a role which eventually could be the much more responsible one of *assistant physician*? Who knows? Questionnaires answered by members of the State Medical Society of Wisconsin suggests they would be. The American Society of Internal Medicine will soon report on its questionnaire to internists seeking their views on the subject. What will be the relation of the physician's assistant to the nurse—in the hospital, in the community health center and in the

physician's office? Why hasn't the nurse, who traditionally has been the right hand of the physician, filled this vital role?

An editorial entitled "Whither Nursing?" in the December 1969 number of CALIFORNIA MEDICINE clearly outlines the issues and some of the dilemmas faced by the nursing profession. In this period of great ferment in matters of health, the role of the professional nurse seems to be changing completely. Let us hope that nurses, nurses' associations, hospital administrators and physicians will recognize the great need for the nurse to expand her basic professional role not in administration but in direct patient care in close alliance with the physician. The wide acceptance by the public of the nurse as a professional person, her recognized ability to expand in capacities and duties as medical science has advanced, and the large number of nurses in this country seem clear reasons for nurses to assume a much larger role in association with physicians in the delivery of modern medical care.

Clearly more help is needed in extending the hand of the physician. Nurses and physician's assistants will play an increasingly vital role with 250 other categories of trained workers in the delivery of medical and health care in the future. The medical profession, which must lead and guide in the efficient and effective delivery of care by all the members of the health team, can serve in this instance by insisting on high educational standards and high quality in practice by all those who have responsibility directly or indirectly for medical and health care.

The hand of the physician needs to be extended, but the prime consideration is that the extension should be such as to be of maximum benefit to the patient and the public. This means deliberate and orderly progress in the respective roles of all those who will serve on the health team.

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# Hyperglycemia and Diabetic Vascular Disease

DIABETES MELLITUS is generally defined today as an inherited disease consisting of two components: First at some stage in the disease there exists an abnormality in the ability to metabolize glucose, a biochemical defect which is ascribed to an inappropriately low secretion of insulin by the pancreas; and second, human diabetes mellitus is characterized by a specific type of vascular disease, which involves the capillaries and arterioles supplying most, if not all, tissues of the body. From a clinical standpoint, and perhaps from a pathogenic point of view as well, it is increasingly clear that it is the vascular aspect of diabetes mellitus that represents the most important of these two components. It is a general experience today that not more than 20 percent of adult patients with overt diabetes—that is, those with fasting hyperglycemia—manifest a degree of carbohydrate intolerance sufficient to require exogenous insulin replacement. Moreover, the complications that result directly from the carbohydrate abnormalities of diabetes—diabetic ketoacidosis and hyperosmolar coma—while dramatic, actually afflict only a very small proportion of adults who have diabetes; and only rarely are such complications the cause of death in the diabetic population. On the other hand it has become increasingly obvious that the vast majority, probably 85 percent, of patients with diabetes mellitus suffer from or die as a direct consequence of the microangiopathic aspects of this disease, *i.e.*, nephropathy, premature atherosclerosis, retinopathy, and gangrene. These devastating effects of diabetic microangiopathy coupled with the increasing realization that the carbohydrate manifestations of diabetes are of themselves rarely of clinical importance have in the past decade caused a renewed interest in the old problem of what is the relationship between the carbohydrate abnormalities and the vascular aspects of diabetes. Are the carbohydrate derangements responsible for the vascular manifestations of genetic diabetes mellitus or, alternately, might the vascular disease itself be primary and the carbohydrate manifestations represent simply a mild complication of diabetes mellitus? Obviously related to this problem of the basic pathogenesis of diabetes is the practical clinical question of whether the control of the carbohydrate manifestations of diabetes

mellitus will delay or prevent the development of the vascular component of the disease.

The latter question cannot today be answered in any dogmatic fashion, but it is a common experience that patients who would be classified as having very mild diabetes from the standpoint of their carbohydrate intolerance, *i.e.*, those whose disease is readily controlled with oral hypoglycemia agents or even with diet alone, develop the vascular manifestation of diabetes mellitus at least as readily as do patients with insulin-dependent, keto-acidosis-prone diabetes. It is certainly safe to state that if “tight” control of carbohydrate metabolism has any influence upon the vascular disease of diabetes, this effect is extremely subtle and has certainly not been demonstrated to the satisfaction of critical observers.<sup>1</sup>

One of the more important obstacles to defining the relationship between the carbohydrate and vascular manifestations of human diabetes mellitus has been a lack of a means of measuring objectively the severity of the microangiopathy. A major advance in this field resulted from studies of the past decade which demonstrated that the underlying lesion of diabetic renal disease is a thickening of the basement membranes or of “basement membrane-like material” surrounding the capillaries supplying the glomerulus.<sup>2,3</sup> As a direct outgrowth of this finding, it has occurred to a number of investigators that by examining a biopsy specimen from suitable vascular tissue, it might be possible to measure the width of the capillary basement membranes and thereby to quantify diabetic microangiopathy. One such approach involved electron microscopic examination of the capillaries supplying the quadriceps muscle.<sup>4,5</sup> From examinations of muscle biopsy material from more than a hundred diabetic patients, the conclusion was reached that thickening of the muscle capillary basement membrane is present in more than 98 percent of patients and so represents a virtual *sine qua non* of adult diabetes mellitus in man. Such quantitative measurements of diabetic microangiopathy have also indicated that there is no detectable relationship between the degree of basement membrane thickening and the severity of the carbohydrate abnormality or the degree of control of the blood glucose level in a given diabetic patient. Another surprising finding of this study was that significant basement membrane thickening was consistently detectable in adult diabetes at the time that hyperglycemia was first observed, a



finding that would suggest that exposure of capillaries to many years of hyperglycemia is not prerequisite to the development of basement membrane hypertrophy. These data would therefore support the contention that the carbohydrate abnormalities of diabetes probably are not responsible for the vascular aspects of this disease.

There are obviously a number of other possible experimental approaches to the question of the relationship between carbohydrate abnormalities and diabetic vascular disease. One such method would be to examine the effect of severe carbohydrate abnormalities on capillary structure in the absence of human genetic diabetes mellitus. It is here that animal models should prove invaluable. As Renold emphasizes in his article which appears elsewhere in this journal, a number of animal models of human hyperglycemia have been developed over the past few years. Very severe carbohydrate abnormalities can be induced in a variety of animals by means of pancreatectomy or treatment with alloxan. Further, hyperglycemia, with or without obesity, can be selectively bred into a specific species.

Some types of hyperglycemic rodents, as Renold notes, are characterized by high levels of insulin, whereas others (as in human diabetes) will show inappropriately low insulin responses to a given glucose level. Such animal models have proven to be very useful in the study of the carbohydrate abnormalities that may accompany hypoinsulinism or hyperinsulinism. On the other hand it is highly questionable whether the second essential component of human diabetes mellitus, that is, the consistent presence of microangiopathy, has ever been demonstrated with either induced or genetic hyperglycemia in any animal. In view of the very real difficulties in studying the pathogenesis of the human diabetic vascular disease, we had hoped that one or several of the inherited types of rodent hyperglycemia might be accompanied by microangiopathy and thereby might also provide a complete valid model for human diabetes mellitus. With this aim in mind we have examined examples of rodent hyperglycemia including the Chinese hamster, the KK mouse, the *obob* mouse and the Egyptian sand rat, and without exception have failed to find significant basement membrane thickening.<sup>5,6</sup> Failure to detect the vascular component of human diabetes in short-lived rodents led us next to examine the effect of severe long-standing hyperglycemia upon muscle capillary

basement membranes in the rhesus monkey. In collaboration with Gibbs of the University of Nebraska we have shown that rhesus monkeys with severe alloxan-induced hyperglycemia for as long as 12 years have consistently failed to show any evidence of basement membrane hypertrophy.<sup>6</sup> In this regard it is noteworthy that recently published data have demonstrated that long-standing alloxan hyperglycemia in dogs does not cause renal capillary basement membrane.<sup>7</sup>

It is perhaps surprising that no species other than man should have developed both the microangiopathy and the carbohydrate abnormalities of genetic diabetes; and, on the reasonable assumption that such a disease probably does exist in nature other than in man, every effort obviously should be made to find an animal counterpart to human diabetes mellitus. At present, however, it is doubtful that diabetic microangiopathy has been shown to accompany hyperglycemia in any sub-human species.

In addition to such animal studies, strong argument supporting the conclusion that hyperglycemia itself is not a factor responsible for human diabetic vascular disease is derived from measuring basement membrane width in patients with severe hyperglycemia due to causes other than diabetes mellitus. Patients with destruction of the pancreas secondary to alcoholic pancreatitis may have pronounced hyperglycemia of many years' duration, and yet we have not been able to find consistent thickening of capillary basement membranes in such patients.<sup>5</sup> In general this observation is in conformity with the clinical finding that it is only the rare individual with pancreatogenous hyperglycemia who shows any clinical evidence of diabetic microangiopathy.<sup>8,9</sup> It is probable that the few examples of diabetic microangiopathy accompanying pancreatic destruction simply represent coexistence of two not too uncommon diseases, pancreatitis and diabetes mellitus.

These studies both in animals and in man have therefore led us to suggest that hyperglycemia *per se* is probably not the cause of the vascular abnormalities of human diabetes mellitus. Finally, we have attempted to approach this question by determining whether patients with the genetic propensity to diabetes mellitus will develop detectable vascular disease before the first evidence appears of diabetic carbohydrate abnormalities. A series of 31 genetically prediabetic patients, *i.e.*, individuals both of whose parents have overt diabetes

mellitus but who themselves show no evidence of carbohydrate abnormality, have been studied. It has been possible to demonstrate readily that in such subjects average membrane thickness is significantly greater than in normal subjects, and moreover; in well over one-half of such prediabetic patients a statistically significant degree of basement membrane hypertrophy is present at the time of biopsy.<sup>5,6</sup> These data would then lend further support to the suggestion that the carbohydrate abnormalities of diabetes mellitus do not cause the vascular disease of diabetes. They raise the possibility that the vascular disease of diabetes mellitus may actually represent an independent and perhaps a primary lesion of the diabetes syndrome.

In summary, electron microscopic studies both in hyperglycemic animals and in hyperglycemia of non-diabetic origin in man would indicate that elevations in blood glucose, even though severe and of long duration, do not themselves produce diabetic microangiopathy or capillary basement membrane thickening. On the other hand human genetic diabetes mellitus regularly leads to clinically apparent vascular disease and can consistently be detected by electron microscopic examination of muscle capillaries. Even in the presence of genetic diabetes mellitus, diabetic vascular disease in man appears to be independent of the severity of the carbohydrate abnormalities of diabetes. Electron microscopic evidence indicates that diabetic vascular disease regularly precedes the appearance of the overt carbohydrate derangements in adult diabetes. The overwhelming clinical importance of the vascular component of human diabetes mellitus makes it particularly important to develop a diabetic animal model in which, as in man, microangiopathy is a major component. It is, however, doubtful whether such a disease has been documented to date in any species but man. The concept which is developed from these conclusions is that it is the clinically important vascular aspect of human diabetes mellitus which is both unique to man and may well play the primary role in the pathogenesis of diabetes mellitus.

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## Antibiotics

ONE OF THE REASONS for so much drug poisoning from antibiotics, is that we learned how to use them before we learned how they worked. The science of antimicrobial drugs until recently was little more than a crude screening process for mold products that could stop growth of pathogenic bacteria without gross injury to animals or human subjects. For many years nothing was known of the chemical reactions that enabled these mold products to stop growth of microbial cells, hence no one could predict whether similar reactions in human cells would be disturbed as well. One reason for this empirical approach to chemotherapy of infection was the unwillingness of drug firms in this country to invest their resources in basic analytical studies of cellular processes. To



the contrary, some companies appeared to flourish from the confusion growing from reactions and resistance to antibiotics, for it seemed to provide reason to offer new drugs with different brand names. Thanks, however, to federal support of research by a number of gifted scientists in this country and elsewhere, we now have a remarkably clear understanding of the fine structure and biochemical activity of bacterial cells, and how they are affected by antibiotics. From this understanding it should be possible to develop bacterial chemotherapy to the point where infections can be treated without drug reactions.

The key to the problem is the discovery and analysis of the bacterial cell wall. From the point of view of chemotherapy, a successful attack there can unloose the corset that holds the bacterial cell together, so that it more or less bursts from the high internal pressure. The chemical structure of the corset is like that of chitin, the substance responsible for the rigidity of the exoskeleton of insects. Sugar chains composed of acetylglucosamine and muramic acid and attached to short peptides are cross-linked to form a net-like polymer known as murein. The cross-linking reaction is carried out by an enzyme that links D-alanine to the peptide of a neighboring chain. Since penicillin is a structural analogue of D-alanyl - D-alanine, it reacts with and irreversibly inactivates the transpeptidase that functions as the cross-linking enzyme. By obstructing the terminal cross-linking reaction, this antibiotic disrupts the integrity of the murein layer and the mechanical rigidity of the cell.

These discoveries by Park, Strominger, and others, have exciting implications to clinicians who treat infections. The action of penicillin on bacterial murein means that it strikes a vulnerable bacterial target that is not present in human cells. As human cells do not contain murein and do not exhibit a cross-linking reaction involving D-alanine, penicillin cannot damage them. Penicillin thus exemplifies the ultimate in selective toxicity: lethal for the microbe and devoid of primary toxicity for the patient. Other antibiotics with the cyclic dipeptide structure of the penicillin group, such as cephalothin, exhibit the same selective toxicity.

In contrast to the penicillins, all other antimicrobial drugs attack vital structures or metabolic processes in bacteria that have a vulnerable counterpart in human cells. Polymyxin B and colistin are cationic detergents that react with phosphate groups in the cell membrane of bacteria so that

the osmotic carrier is disturbed and leakage of amino acids, purines, and pyrimidines occurs. Amphotericin B also injures the cell membrane, but through an affinity for sterols present only in fungi rather than bacteria. It is possible that the nephrotoxicity of these drugs is related to similar injury to the cell membranes of kidney epithelium. In addition, the hemolytic reactions consistently observed in patients given amphotericin B intravenously appear to result from binding of this drug to sterol groups on red cells.

The remaining drugs used for treating human infections act within the cell on synthetic and metabolic processes. The antibiotics in this group all inhibit protein synthesis. Chloramphenicol, the most toxic for humans, prevents attachment of messenger RNA to ribosomes; the tetracyclines and lincomycin interfere with binding of transfer RNA to ribosomes; and the aminoglycosides (streptomycin, kanamycin, neomycin) attach to the ribosomes and permit incorporation of incorrect amino acids in peptide chains. The effects of chloramphenicol on hemoglobin synthesis in man undoubtedly reflect the same disturbance in human cells that the drug produces in bacterial cells. Similarly the hepatotoxicity of the tetracyclines, and their ability to exaggerate azotemia, are also accountable through their ability to interfere with protein synthesis. The primary toxicity of streptomycin and kanamycin is on the eighth nerve but too little is known about the nature of this injury to speculate on its mechanism.

It is clear, therefore, that penicillin stands out from all other antibiotics in its freedom from primary toxicity in man simply because it has no biochemical target to damage. It is not surprising that penicillin can be given intravenously in doses of 60 to 80 grams with no discernible harm. Even in patients with kidney insufficiency, the toxicity from large intravenous doses is due to the potassium in penicillin, rather than to the antibiotic itself. For this reason, future hope for harmless antibiotics lies in the replacement of other antibiotics through the development of the penicillins. Research along these lines must take two major directions: a broadened antimicrobial spectrum and elimination of allergy.

Thanks to the ingenuity of the British chemists Batchelor, Dewdney, Feinberg, and Weston, exciting progress has been made in both directions. Their isolation of the penicillin nucleus 6-amino-penicillanic acid (6APA) has been followed by



brilliant success in widening its spectrum through modification of the side chain attached to 6APA. The first major development in extending the spectrum came with their synthesis of methicillin by the introduction of two methoxy groups into the side chain so that 6APA could be protected from hydrolytic inactivation by the penicillinase of resistant staphylococci. More recently they found that attaching an amino—or a carboxy—group to the side chain produced two compounds with greatly increased activity against those Gram-negative bacilli that had been clinically resistant to penicillin. Alpha-aminobenzylpenicillin (ampicillin) has been of great value in the treatment of *Salmonella*, *Proteus E. coli*, and *Hemophilus influenzae* infections, while the synthesis of alpha carboxybenzylpenicillin (carbenicillin) has made available, at last, a nontoxic drug that can be used effectively in serious *Pseudomonas* infections.

Isolation of 6APA also led to a search by its discoverers for a non-allergenic penicillin. At first 6APA was thought to be allergenic itself and hence that a nonallergenic penicillin was unlikely, but later studies by Batchelor's group disclosed that an impurity was responsible for allergy. This impurity is a conjugate of 6APA or benzylpenicillin with a protein (D-benzylpenicilloyl protein) and probably develops during manufacture. When the impurity was removed by passage through a sephadex column or by dialysis, neither benzylpenicillin nor 6APA was allergenic. This discovery and others, on the immunochemistry of penicillin allergy, offer substantial hope for the solution of the immunologic disturbances that have occurred from the use of penicillin.

In my opinion, the opportunities are so good for the eventual production of nontoxic penicillin with a universal spectrum of antibacterial activity, that other antibacterial drugs will have little usefulness. The achievement of this important goal in medicine can only come about, however, from support of research at all levels of chemotherapeutic development involving the biochemist, microbiologist, immunochemist and clinical investigator. Unfortunately the tragic restriction of federal support for medical research of this type will hold back seriously the progress that could be made in eliminating harmful reactions from antibiotic therapy.

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## On a Definition of Health

THE REPORT OF THE American Medical Association's Committee on Planning and Development faces up to the important question of what is to be today's working definition of health and what is to be the role of the organized medical profession with respect to it. This report is now undergoing review by state and county medical societies and its recommendations are to be considered by the appropriate Reference Committee at the AMA Convention this June. The need to agree on a definition of health is obvious. The need becomes pressing when one considers the mounting national concern with health and the bald fact that health care is already a \$60 billion a year industry that is still growing and soon to become the largest such enterprise in the nation.

The Committee's report calls for the AMA to adopt officially the World Health Organization definition:

*"Health is a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity."*

The thought of such an all-encompassing definition with all its ramifications in health care stuns many physicians and other health care personnel. The traditional view has been that health means the absence of illness and that the aim of the practitioner is to restore this "health" to the afflicted patient. The word itself derives from "whole" and to heal really means to make whole. Recently, however, the concept of whole in health has been gaining significantly. Medical progress has shown that to be healthy requires that a person be in satisfactory adjustment with many and various aspects of his internal and external environment which affect him and with which he must interact. This goes somewhat beyond just the wholeness of his mind and body. It includes his physical, social, economic, cultural and even political circumstances and environment. That this is true is becoming quite clear to anyone who seeks to provide health through health care services in the urban or rural ghettos, for example, where quite evidently personal health is inseparable from the whole situation. In the further dimension of the closed earth system and its problems of population, resources, pollution, ecological balance and human behavior, the sameness of *health* and *whole* takes on yet a new meaning and a new and very pertinent reality.

The traditional view of health and healing is certainly inadequate in this kind of world. The broader WHO definition much more nearly fills the bill.

As a corollary to accepting this definition of health, the AMA Committee on Planning and Development goes on to recommend that "AMA adopt an active role and take the initiative in developing *all* plans and programs for health care in *all* their ramifications and that it encourage and assist state and county medical societies to do the same at their respective levels."

This, too, is a bold recommendation. Yet there is really no alternative for a profession which professes primary responsibility for health and for the health team in today's society. To be sure, medi-

cine cannot do it alone. Multidisciplinary action, unprecedented cooperation among health professionals and new roles for many physicians will be required. But this is nothing new for physicians. The specifics can be spelled out as the problems are more precisely identified. The important thing is to make an imaginative and determined start.

The AMA House of Delegates should take the bold step. It should recognize the definition of health for what it has come to be in today's world. It should set the AMA on an exciting new course of innovation and leadership. This is clearly in the interest of the public, the profession, and perhaps even human ecology. In today's jargon it will make the AMA much more *relevant* as well as much more effective.

## Clinical Note

# Don't Use the Wrong Vitamin K

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■ *The emergency use of vitamin K is essentially limited to the reversal of drug-induced hypoprothrombinemia. In patients with adequate liver function, phytonadione acts promptly and predictably in this capacity whereas the derivatives of menadione counteract coumarin drugs only slightly or not at all. It is dangerous to rely on menadione analogues, and these drugs should be removed from emergency room drug stores.*

MENADIONE AND ITS water soluble salts (Figure 1), marketed between 1939 and 1941, served an important role in the prevention of hypoprothrombinemia resulting from a simple lack of vitamin K. During the decade which followed, these preparations proved very effective in the treatment of cholemic bleeding due to biliary tract obstruction or fistula, hypoprothrombinemia associated with other malabsorption syndromes, and hemorrhagic disease of the newborn. These vitamin K substitutes gained a strong foothold in clinical practice, became loosely identified as "vitamin K," and are still widely used today.

Meanwhile, a new prothrombinopenic state made its appearance with the introduction of oral anticoagulant drugs. It was soon noted that the menadione derivatives, lacking as they do the phytyl side chain of the parent vitamin K compound, were relatively ineffective in reversing the coagulation defect induced by the coumarin drugs. Indeed, several investigators suggested that menadione and its analogues are devoid of anticoagulant activity,<sup>1,2,3</sup> while others reported

these agents to be only slightly and unreliably effective in counteracting drug-induced hypoprothrombinemia.<sup>4,5,6</sup>

By contrast, phytonadione (vitamin K<sub>1</sub>) was found to be strikingly effective in opposing the action of dicoumarol and its congeners and superior to menadione in correcting other forms of

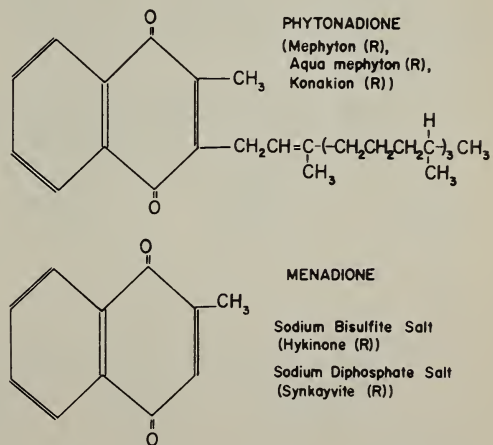


Figure 1.—The structural formulae for phytonadione and menadione.

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hypoprothrombinemia. These findings<sup>7,8,9,10</sup> led to the development and marketing of four phytonadione preparations—tablets and an emulsion for intravenous use (Mephyton®) and an aqueous suspension for intramuscular use (Konaktion®) in 1952, and a colloidal solution for all parenteral routes (Aquamephyton®) in 1960.

With increasing use of the coumarin drugs, the treatment of hemorrhage due to an excessive anticoagulant effect has emerged as a common indication for vitamin K therapy. At times it is of utmost importance to restore the prothrombin time to normal as quickly as possible in patients receiving anticoagulants who are bleeding, either spontaneously or from trauma, and in those being prepared for emergency surgical operation. The control of drug-induced hypoprothrombinemia is essentially the only indication for emergency vitamin K administration. There is no doubt that phytonadione, vitamin K<sub>1</sub>, is the drug of choice for this purpose. Unfortunately, this information has not reached clinical application in many hospitals and clinics in this country. The menadione derivatives are still widely distributed and sometimes used in a misguided effort to correct an excessive drug-induced hypoprothrombinemia.

It is the three-fold purpose of this communication to document again the superiority of phytonadione over one of the menadione salts as a coumarin drug antagonist, to report a survey of available vitamin K preparations in 100 medical emergency rooms, and to urge that menadione and its derivatives be removed and replaced by phytonadione in all hospital and clinic emergency room drug stores.

## Report of a Test Case

The anticoagulant antidotal effectiveness of menadiol sodium diphosphate (Synkayvite®) and phytonadione were compared in one adult male volunteer by sequential administration with warfarin, (Coumadin®), in a fixed oral daily dose of each drug, as shown in Table 1. A very large dose of menadiol sodium diphosphate, 300 mg (60 tablets) per day, was required to counteract a one-fold dosage increase in warfarin, from 10 to 20 mg a day for seven weeks. By contrast, 50 mg (10 tablets) of phytonadione each day effectively counteracted a 30-fold increase in warfarin dosage, from 10 to 300 mg a day during the following seven weeks.

## Survey of 100 Hospitals

The charge nurses in the emergency rooms of 100 general hospitals in Los Angeles were contacted by telephone to learn what vitamin K preparations were available for immediate use. Phytonadione was found in only half the hospitals surveyed (Table 2). One or more of the menadione derivatives were stocked in 87 hospitals. Eight hospitals reported no vitamin K preparations in their emergency room drug stores.

## Discussion

The disodium salts of menadione, containing the naphthoquinone nucleus but not the phytyl side chain of phytonadione (Figure 1), have been useful vitamin K substitutes in the past, but they do not meet the more recent and pressing need for a potent antidote for the oral anticoagulant drugs.

TABLE 1.—*The Antidotal Effectiveness of Menadiol Sodium Diphosphate and Phytonadione Against Warfarin in One Human Subject*

Warfarin (Coumadin®) mg/day	Menadiol Sodium Diphosphate (Synkayvite®) mg/day	Phytonadione (Mephyton®) mg/day	Days of Observation	Prothrombin Tests by the Quick Method	Average Prothrombin Time in Seconds
10			74	64	22.8
20	300		49	49	26.5
300		50	51	51	23.1

TABLE 2.—*Vitamin K Preparations Available in the Emergency Rooms of 100 Los Angeles Hospitals*

	Menadiol Sodium Diphosphate (Synkayvite®)	Phytonadione (Aquamephyton®)	Menadiol Sodium Bisulphite (Hykinone®)	Menadione	Phytonadione (Konaktion®)	None
Number of Hospitals*	84	50	8	3	1	8

\*Two or more preparations were available in 45 hospitals.

Menadione derivatives are potentially dangerous when they are the only vitamin K preparation available in medical emergency rooms. In an effort to arrest a serious coumarin drug-induced hemorrhage, several hours may be lost before it is realized that a menadione analogue has not returned the prothrombin time to a safe range.

James et al<sup>6</sup> demonstrated conclusively that intravenous doses of 64 to 500 mg of menadione and menadiol sodium diphosphate failed to reverse the effect of a single large dose of dicoumarol in 70 patients, whereas similar doses of phytonadione accomplished this objective in less than 24 hours in all except one of 26 patients. There can be no question that phytonadione is the drug of choice and the only drug recommended to reverse an excessive degree of drug-induced hypoprothrombinemia.

An intravenous dose of 5 to 50 mg of phytonadione will restore the prothrombin time to normal or a safe range in 4 to 24 hours in patients with normal hepatic function.<sup>6</sup> Five or 10 mg should be chosen to correct excessive hypoprothrombinemia, with or without a minor hemorrhage such as hematuria, when continued anticoagulant therapy is anticipated. This may be given with success by the oral or a parenteral route. Fifty mg of phytonadione should be given intravenously\* in the treatment of a serious hemorrhage. The intramuscular route should not be relied upon to control severe bleeding,<sup>11</sup> and all intramuscular injections should be avoided when a severe deficiency of coagulation factors exists.

Whole blood or plasma should also be given in the event of a rapidly falling hemoglobin level, to restore blood volume and replace immediately the vitamin K-dependent clotting factors (II, VII, IX, X) during the latent period of phytonadione's action. In cases of massive coumarin drug over-

dosage, repeated injections of phytonadione may be required over several days to control a resurgence of coumarin drug effect. There is little storage of phytonadione in body tissues, and the metabolic life of the coumarin drugs extends over several days.<sup>12</sup>

The aqueous colloidal suspension of phytonadione, Aquamephyton®, has proved to be remarkably safe intravenously if administered slowly, at a rate less than 5 mg per minute. Three cases only of circulatory collapse following intravenous administration, including one death, have been reported to the manufacturer during the past decade.<sup>13</sup>

#### TRADE AND GENERIC NAMES OF DRUGS

*Hykinone*® . . . . . menadione sodium bisulfite  
*Synkayvite*® . . . . . menadiol sodium diphosphate  
*Mephyton*®, *Aquamephyton*®, *Konakion*® . . . . . phytonadione  
*Coumadin*® . . . . . warfarin

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\*Aquamephyton® is the only phytonadione preparation marketed for intravenous use.

# The Physician and Comprehensive Health Planning

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COMPREHENSIVE HEALTH PLANNING (Public Law 89-749) enacted by the 89th Congress in 1966 is one of the most important single pieces of legislation affecting public policy in health in the history of the United States. Although more than a score of other health and health-related laws were passed by the Congress that year, including Medicare, Medicaid and Regional Medical programs (which received more attention and public debate), the so-called Partnership for Health Act will probably have a greater effect on the total spectrum of future health care services, organization, financing, distribution and delivery than all of the others combined. Those physicians who tend to look upon the Medicare law as the turning point in public policy regarding health are merely viewing a small arc of the wide circle of events which already have been and are yet to be generated as a consequence of this legislation which passed virtually unnoticed and unheralded in the plethora of health legislation of the '60s.

The Comprehensive Health Planning and Public Health Service Amendments of 1966 did indeed formulate the principles for the design of a framework around which new directions and courses of action would be developed for the health care of the American public. But, more, it introduced new concepts and structures which would assure the broadest voluntary involvement of community forces and institutions in its implementation. If there are any doubts regarding the intent of Congress, a single sentence in the preamble to the law should dispel them. It reads:

"The Congress declares that fulfillment of our national purpose depends on promoting and assuring the highest level of health attainable for every person, in an environment which contributes positively to healthful individual and family living."

Although events and experience over the past three years have raised questions and created frustrations concerned with the nature of the "partnership," the law has at least produced the beginnings of an alliance among the various elements and components of the private and public sectors and the various levels of local, state and federal governments. This amalgam is beginning to yield evidence of cooperative and coordinating efforts to "plan together" and to "plan comprehensively" in order to be concerned with all of the problems which affect the "health environment" of the public. Thus, for the first time, all factors relating to health are being approached as part of a total problem rather than as fragmented or single parts existing by themselves. To comprehend how all-encompassing this piece of legislation is, and how closely its activities are intertwined with the professional obligations and social responsibilities of the medical profession, one need only realize that the areas of personal health services, health facilities, environmental health, mental health and manpower are included in the scope of responsibilities of the law. Its greatest innovation, however, rests in the fact that, for the first time, it accords to the public, as consumers, a potent voice in the planning decisions to be made.

Comprehensive health planning therefore provides the meeting ground where representatives of the health care professions come together with representatives of the public not as patients but as

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peers in the planning process. Although the concept of planning is not a new one, the term *planning process* has taken on new meaning to the individuals, organizations and communities engaged in this process, since many of those involved bring to the planning arena a range of experience ranging from minimal to maximal exposure to and understanding of the issues with which they are confronted. For physicians, particularly, the process offers opportunities for contributing to community efforts to identify health problems, to assist in securing appropriate and valid information about such problems, to aid in establishing broad goals and specific objectives with reference to alternative solutions, and to evaluate the results of efforts made to deal with them. Like the others whose opinions they will share, physicians must begin to look at old problems in a new way, to reexamine existing patterns, to evaluate the evidence brought to their attention, and to consider or embark upon new ways of doing things. They will be involved in a never-ending self-renewal cycle of events which must take into account all the community resources and facilities and the coordination of such resources, as well as the creation of new approaches and mechanisms where they are needed for resolving the problems under study.

The basic implementing sections of comprehensive health planning legislation illustrate the wide scope of activities and responsibilities with which program participants and the total community must become familiar. They are:

*Section 314(a): Statewide Comprehensive Health Planning*—which provides for the establishment of a single state agency to develop a comprehensive health plan for the state to provide comprehensive health services, both public and private. The agency in California is the State Department of Public Health. Its advisory body, the State Health Planning Council consists of providers and consumers, with the latter constituting a majority.

*Section 314(b): Areawide Comprehensive Health Planning*—which provides federal funds to public or non-profit private agencies to engage in organizational and comprehensive health planning efforts for a given geographic area of the State. Nine such geographic areas have been designated by the State Health Planning Council in California.

*Section 314(c): Grants for Training, Studies and Demonstrations*—which provides federal funds for programs which are intended to develop new kinds

of persons to meet manpower needs of comprehensive health planning agencies, both statewide and areawide.

*Section 314(d): Block Grants for Comprehensive Health Services*—which provides for the elimination of the traditional funneling of federal funds to state public health and mental health departments through categorical grants, and establishes a block grant system.

*Section 314(e): Project Grants for Health Services Development*—which provides grants to meet the health needs of the people. Applications for funds must be reviewed and approved by the state agency for conformance with such plans as have been developed by the agency. Final funding decision rests with the federal agency; very few of such grants have been funded in California due to lack of money.

Just as the California Medical Association assumed a leadership role in cooperating with and implementing Public Law 89-239 (Regional Medical Programs for Heart Disease, Cancer and Stroke), it took the initiative in calling the attention of physicians to the potentials for service and their professional contributions in implementing the provisions of Public Law 89-749. Even before the program got off the ground in California, the California Medical Education and Research Foundation of the California Medical Association sponsored (in November, 1967) a 14-state regional conference on "Future Directions and Decisions in Medical Care." This conference, which was devoted to a discussion of the law and to the role of the medical profession was followed in July, 1968, by a regional conference on the "Planning Process" and, in November, 1969, by a regional conference which concerned itself with the "Progress, Problems and Perspectives" of the legislation.

In California the State Health Planning Council (originally constituted with 13 members and later expanded to a 21-member group) supervises the comprehensive health planning functions of the State Department of Public Health. It has developed and adopted guides and policies for comprehensive health planning activities by areawide agencies and has designated nine geographic areas for health planning, eight of which have been funded to date.\* Committees of the State Health Planning Council have been appointed and charged

\*The areas, and the cities of their headquarters, are: North Coast, Eureka; Superior California, Chico; Golden Empire, Sacramento; Bay Area, San Francisco; North San Joaquin, Stockton; Central California, Fresno; Mid-Coast, Salinas (not yet funded); Southern California, Los Angeles; San Diego-Imperial, San Diego.

with responsibilities in the fields of personal health services, environmental health, health facilities, health manpower, and health information systems. Special task forces have been established to deal with specific problems such as manpower, emergency medical care and outpatient care. A variety of liaison activities have been initiated to help assure the coordination of efforts of statewide private and public agencies. These include Air Resources Board, California Commission on Aging, Office of Economic Opportunity, Department of Alcoholic Beverage Control, water resources and other departments and agencies of state government. The incorporation of separate legislatively established committees, previously responsible for Hill-Harris (Burton) allocations and for mental retardation activities into comprehensive health planning, has resulted in further coordination of statewide planning efforts. The recent enactment of California's AB 1340 provides a voluntary basis for area-wide planning of facilities. It has resulted in giving areawide comprehensive health planning agencies additional authority and responsibilities with regard to licensing hospitals and facilities. This role was formerly carried out by the Voluntary Health Facilities Planning group but in 1969 this activity was merged to Comprehensive Health Planning. Guides for implementation of this responsibility were approved by the State Health Planning Council in January. Now in development is a state plan for health and a work program which will establish goals and priorities for statewide planning efforts.

In all of these activities, county medical societies and their members have played a most impressive role by bringing together representatives of a cross-section of their communities for the purpose of establishing county as well as areawide committees to carry out the intent of Public Law 89-749. It is largely due to their efforts and to the encouragement given to them by the California Medical Association that California has acted so quickly and progressed so far in this program. It is expected that physicians will continue to support these efforts, in the realization that local community planning is the key to the development of a rational state plan for health. There is universal recognition of the fact that, for the first time, comprehensive health planning provides communities with the opportunity to plan on the basis of local needs and local assessments of the health problems in their respective areas. If this effort should fail, they

should have no doubt that decisions will be made for them by other legislative actions.

The efforts in California thus far have been largely concerned with the organizational phase of implementing P.L. 89-749. Nevertheless, significant beginnings have been made in the planning process itself; problem areas are being identified, information is being collected and evaluated, plans are being formulated and goal and priorities are in the formative stages of development. There are yet a number of problems to be resolved, but the evidence on hand is that California is forging ahead. The problems that exist vary from one area to another, and some of them will take time and patience to resolve. Some of them will find solutions locally; some will have to be resolved by the State Health Planning Council; and some must look to legislative changes in the law by Congress for solution. Intrinsic and extrinsic factors and relationships have created uncertainties, frustrations and even head-on collisions with other health programs and activities which have not as yet been assigned to or coordinated with comprehensive health planning by the Congress. Lacking are federal administrative policies and firm guidelines relating to comprehensive health planning, the health programs of the Veterans Administration, Regional Medical Programs, Office of Economic Opportunity, Model Cities and Indians Affairs, for example.

Whether some or all of these programs eventually come within the purview of comprehensive health planning activities or remain as individual entities is perhaps less important at this time than the need for all programs to accept the responsibility of developing liaison and cooperative relationships with a program which is committed to stimulating and conducting comprehensive health planning for all segments of the American public. There appears to be no reason why the capabilities and commitments of each program cannot be utilized to achieve the intent of Public Law 89-749 whose purpose is to create "an environment which contributes positively to healthful individual and family living."

Therefore all physicians in the private practice of medicine can aid in these efforts in behalf of their patients and their communities. This will give demonstrable evidence of the medical profession's support of the concept of voluntary comprehensive health planning. The experience in California in the past three years must be taken as an earnest of that support.



## *In the Forefront*

# Interagency Council on Drug Abuse

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CALIFORNIA INTERAGENCY COUNCIL on Drug Abuse (CIACODA) — established in October 1968 by California Medical Association in cooperation with the State of California and the Parent-Teacher Association—is a clearing house for the exchange of information and techniques found useful in combatting the state's drug abuse problem.

The Council is composed of six statewide task forces—treatment, research, education, administration of justice, legislation and government, youth — each focusing upon its specialized field of interest within the overall problem. The six task forces convene as the Council to facilitate communications among the six and to insure against imbalance among the diverse points of view and special interests represented.

### *Functions*

In a state as large and populous as California, the primary need of the hundreds of organizations and programs of drug abuse prevention, education, treatment, research and rehabilitation is for information. Eighteen meetings of the various task forces were held in the first year of CIACODA operation, providing a means for some two to three hundred persons, representing dozens of organizations, to share information about drug abuse programs and activities. In addition, many of the organizations represented have published useful information in their own newsletters and disseminated materials to their membership.

### *Coordination*

Although coordination of the efforts of the many organizations and individuals involved is only now beginning, much already has been accomplished by joint effort. Four member organizations have acted together to bring about the publication of a medically approved brochure for statewide distribution. Surveys are now available of all drug abuse treatment and referral resources in the state.

Educational programs are being surveyed and a comparative study is under way to determine the differential effectiveness of various educational methods. Coordination of drug abuse materials is being attempted: some 3,000 pieces of drug abuse literature, including bibliographies and motion picture information, have been reviewed and are on file in a clearing house. Samples of approved and recommended brochures and booklets are available.\* Many scientific papers and books are also available and single copies are given or lent to professional and lay groups and individuals. Approximately 10,000 requests for material of this kind have been filled to date.

### *Consultation*

A task force on Drugs and Alcoholism of the California Council on Criminal Justice is the latest organization to seek consultation from CIACODA. Consultation has been provided also to many local and county groups, to the Advisory Panel on Drug Abuse Education, the Advisory Panel on

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\*For example, the medically approved text of the "Health Forum" publication "Damaging Effects of Drug Abuse" has been reprinted (with CMA permission by San Mateo Citizens' Council on Drug Abuse as a brochure, and under the title "Drug Abuse" by the Department of the Youth Authority.



Drug Abuse Research, and the Drug Abuse Information Center, all three of which were set up by statute. In addition, CIACODA is an officially recognized advisory body to the Governor. The chairman has testified repeatedly before congressional and state legislative hearings.

Another activity was a joint survey carried out by CIACODA and the Drug Information Center at UCSF Medical Center to supplement the Center's third annual report to the Legislature. CIACODA is currently cooperating in a Department of Mental Hygiene Survey.

### *Representation*

CIACODA has received cooperation and encouragement from a wide range of organizations and agencies, public and private, concerned with drug abuse. The work of the Council is done by the task forces, and membership, meetings and participation are generally open to all interested persons and organizations. Three representatives of each task force meet together as a council. These are specified as follows:

*Administration of Justice:* The president of the California Association of Peace Officers, one designee of the Bar Association, one designee of the Judicial Council.

*Legislation and Government:* One representative of the Executive Branch, one designee of the Speaker of the Assembly, one designee of the President *pro tem* of the Senate.

*Education:* One representative of the schools, one representative of the community, and one representative of the media.

*Treatment:* The presidents of the California Conferences of Local Health Officers and of Directors of Mental Health and a representative of the California Medical Association.

*Research:* Three nationally known researchers in drug abuse, elected by the task force, (which includes virtually all of the prominent researchers in California).

*Youth:* Three young people elected by the task force, (which includes youth from a wide range of segments of the population).

In addition, many self-help groups of former drug users, all the relevant official agencies of government and a large number of professional organizations throughout the state have contributed to the initial impetus of CIACODA.

### *Funding*

Each of the organizations and associations represented on the CIACODA has absorbed the expenses of its representative in the first year of operation. The California Medical Association has borne the administrative cost and has provided a part-time coordinator. CIACODA has also had the consultation and support of the CMA Committee on Dangerous Drugs. Consultation has also come from the state departments of Education and Public Health, and meeting space has been provided by the Department of Public Health, the California Teachers Association, several county health departments, and others.

As CIACODA enters its second year of operation, limited funds are being made available through the Council on Criminal Justice and possibly some from the American Medical Association and from the National Institute of Mental Health. The Drug Abuse Information Center and the Drug Abuse Education Advisory Panel are both funded by statute, but with decidedly limited budgets. The Drug Abuse Research Advisory Panel, also set up by legislative action, is not funded at all. In each instance, through overlapping membership and with much consensus of objectives, the corresponding task forces of CIACODA seek to aid the work of these groups and plan to continue to cooperate with each of them.

### *Projects*

Each task force has undertaken one or more projects in the past year. For example, the task force on treatment is in the process of publishing a manual and flow-chart for drug abuse treatment facilities. It is planned to distribute this (as an appendix to the toxicology manual) to every hospital emergency room, mental health center and "free" clinic in the state. In the coming year CIACODA plans statewide conferences on community drug abuse programs (for those engaged in or planning community programs) and possibly conferences on nalorphine testing, and on methadone maintenance. Publication of additional materials is under consideration. Expansion and support of minority-group representation, employment of former users, and activities proposed by the task force on youth are additional projects, and consultation and coordination efforts will be increased.

# Physician's Assistants

## A Socio-Economic Report of the Bureau of Research and Planning, California Medical Association

FOR SEVERAL YEARS, the medical literature has been filled with articles citing statistics on the crisis in health manpower. For example, merely to maintain the 1960 ratio of physicians to population in 1970, it will be necessary to have a net growth of about 20 percent of the 1960 supply of 257,000—an increase of more than 50,000 doctors.<sup>1</sup> In 1900 there was one allied health worker for each physician. In 1965 the ratio was about ten to one; and today there are approximately 13 allied health workers for each physician. These allied health workers fall into 268 classifications, and in December 1965, according to the Department of Health, Education and Welfare, nearly three million people were employed in the health services and related fields.<sup>2</sup> At that time, the health services industry was the third largest in the nation; and if the total investment in health care increases as predicted during the next decade, the health field may rank first among American employers, with almost twice as many personnel as are currently employed. In the categories of aides, orderlies, and attendants alone, 410,000 persons were employed in 1963; by 1966, the number had risen to nearly 475,000.<sup>3</sup>

The ever-expanding demand for health services, attributable to population and economic growth, technological-scientific advances, and rising public expectations, has resulted in a compounding of manpower problems.<sup>4</sup> The expansion of health services, growth of prepayment, and increasing importance of health as a social value during the past two or three decades have paved the way for this manpower crisis; and recent legislation and the establishment of new programs such as Medi-

care have focused professional and public attention on health manpower needs.<sup>5</sup> With the changes taking place in medicine today due to rapid technological advances and the greater utilization of health care services by the consumer, it is certain that ever greater numbers of properly trained allied health personnel, as well as of physicians, will be needed in the future.

The traditional means of meeting the health manpower shortage has been to increase the number of places in medical schools but it is obvious that this measure will not be adequate to meet the predicted shortage of one million additional health workers expected by 1975.<sup>6</sup> New types of personnel will have to be developed to meet the increasing demand for comprehensive health care.

Delegation of specific tasks is one way of utilizing existing manpower effectively; and if new types of personnel are established, even greater efficiency may be achieved. "If a doctor can delegate tasks to a nurse or a properly trained pediatric nurse associate or pediatric assistant, and if on down the line there is a delegation of chores to lesser trained persons who are capable of properly performing specific tasks, the resultant effect will be a greater availability and distribution of high quality health care services."<sup>7</sup> Many existing positions could be staffed by personnel with less formal training than is now required, eliminating one type of waste of manpower.

One of the most promising categories of new personnel is the "physician assistant," who would handle routine duties, requiring some medical skill, that today take up much of the doctor's time.

A good example is the Physician's Assistant Training Program begun at Duke University in 1966. Under this career program individuals with a background in health care, such as medical corps-

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men and Licensed Practical Nurses, are trained to assist the physician in carefully defined areas of both clinical and research practice. In patient care, the physician's assistant, "learns to draw blood, start and regulate intravenous infusions, intubate the GI tract, and do other procedures classically performed by the doctor. He is trained to monitor vital signs, give medications, and keep progress reports, skills classically performed by nurses. He is also taught to operate certain diagnostic and therapeutic instruments, such as an EKG machine and respirator, as well as to carry out routine laboratory studies commonly done by technologists. The program calls for intensive training in areas which will complement available health team talents without attempting to replace available talents."<sup>8</sup>

The physician's assistant curriculum takes two years of pre-clinical and clinical work after high school graduation. Graduates of the program will specialize in one of six clinical areas, such as renal dialysis or cardiac catheter lab, and will work under the supervision of one or more physicians in a hospital, medical center, or private office or group. Salaries for the physician assistants already trained average slightly more than \$10,000 per year. Many medical schools across the country have observed the Duke University program with interest, and at least ten others have similar programs under way or in the planning stage.

One largely untapped source of physician's assistants is the use of medical corpsmen released from the armed forces. Programs are now being started "to document the Army corpsmen's experiences and to cooperate with civilian institutions in the same area, and link civilian needs with trained personnel as they leave the Army." Already, the Bureau of Prisons employs 125 former corpsmen as physician's assistants in 26 Federal prisons. Their greatest contribution is in "extending the physician by their day-to-day functions in the area of diagnostic evaluation and the treatment of medical and surgical conditions." These physician's assistants perform an estimated 70 percent of all direct patient care functions, including parts of physical examinations, routine clinical laboratory tests, and physical therapy.<sup>9</sup>

Another program, funded by a grant from the Office of Special Manpower Programs of the U.S. Department of Labor to the Santa Clara Medical Society, has the initial goal of helping at least 50 discharged medical corpsmen in Santa Clara Coun-

ty to find jobs or to further their education in the health fields. Objectives for the first year of operation are to:

1. Provide these discharges with counseling services by referral and direct contact with representatives of local health and education agencies;
2. Evaluate current skills of the discharges and identify training or educational needs to bring the discharges up to a level of employability in a health field;
3. Work with the local health and educational institutions, including the Veterans Administration, to arrange for training and/or job placement, and
4. Work with appropriate state and local agencies to modify licensing procedures to make provisions for the utilization of these trained discharges.<sup>10</sup>

A similar program, called Medex, is being undertaken by the Washington State Medical Association Education and Research Foundation and the Department of Preventive Medicine of the University of Washington Medical School. The purpose of Medex is to give former corpsmen three months of intensive training, followed by a 12-month preceptorship with selected physicians.

Since about 30,000 corpsmen are discharged annually, some with quite extensive medical training, programs of this type may prove quite valuable in helping to resolve some of the problems of manpower shortages.<sup>11</sup>

A more specialized career program, started by San Francisco's Pacific Medical Center and City College of San Francisco, will train students as orthopedic assistants. Graduates of the two-year program will assist the orthopedic surgeon in patient care in the cast room, operating room, emergency room, office, and in the application of traction. The program has the support of the American Academy of Orthopedic Surgeons, and is funded by a grant from the United States Public Health Service.<sup>12</sup>

The specialty of pediatrics, with the active participation of the American Academy of Pediatrics, has fostered more programs to date than has any other area of medicine. The shortage of pediatricians is particularly acute; by 1980, there will be an estimated 76 million children in the United States. To maintain the 1961 pediatrician/child ratio of 151/100,000, almost 115,000 pediatricians would be needed, or 100,000 more than are presently in practice.<sup>13</sup> In June of 1969, the execu-



tive board of the American Academy of Pediatrics approved the establishment of a Division of Allied Child Health Manpower. The board also endorsed the official position of the Academy concerning allied child health manpower: "that the physician may delegate to a properly trained individual working under his supervision the responsibility of providing appropriate portions of health examinations and health care for infants and children."<sup>14</sup>

The Academy has identified three categories of allied health personnel: Pediatric nurse associates, pediatric office assistants, and pediatric aides.<sup>15</sup> The pediatric nurse associate will be an RN whose activities will be largely centered on direct patient care. The pediatric office assistant will have completed two years of college, and will be supervised by the physician or the nurse associate in such duties as hearing and vision screening and education-counseling. The pediatric aide, usually trained on the job after high school graduation, will help the physician, nurse associate, or pediatric office assistant in routine or non-skilled tasks.

The three types of allied health workers outlined above will be developed under the American Academy of Pediatrics' Allied Child Health Manpower Training Program. However, other programs are being established at medical schools around the country to train new types of pediatric health professionals. One of the most important of these is the Child Health Associate Program at the University of Colorado. The curriculum will take five years after graduation from high school, including two years of college as a prerequisite, two years of clinical instruction, and one year of internship, and will cover the basic sciences and clinical experience in many different settings. Study of the social, behavioral, psychological, and ecological aspects of health care for children will be included in the curriculum. Graduates will have "problem-solving and decision-making capabilities in certain areas of child care which will closely approximate those of physicians. They will be qualified to diagnose, prevent, and treat most of the common medical problems of childhood. On completion of the course of study, the Pediatric Associate will have the knowledge and skill to care for approximately 80 percent of the patients seen in a typical pediatric practice but with emphasis on preventive pediatrics and in keeping children healthy, both physically and mentally."<sup>16</sup>

Programs such as those discussed here cannot be successful without the sanction of organized

medicine, whether national, state, local, or specialty. The Councils on Health Manpower and Medical Education of the AMA are helping to develop guidelines for the education of the physician assistant, in consultation with the program directors. According to Joseph Donovan, Executive Director of the Santa Clara County Medical Society and consultant on health manpower to the U.S. Department of Health, Education and Welfare, "The road to take is probably through the state medical associations recognizing there is a manpower shortage and it's going to get worse." It is also necessary for organized medicine to identify local needs and set local priorities. Donovan also stated that, "... the leadership for doing it on the state basis should come from the incentive and encouragement of the AMA."<sup>17</sup>

It is possible that there may be problems in the acceptance of new types of health professionals by physicians, by nurses, and by the patient. Physicians may be concerned about the possibility of malpractice suits, of assistants setting up their own practices, or of losing personal contact with their patients. Licensing and certifications standards, as well as new legislation, should be adequate to cope with the first two problems. And by freeing the doctor from routine tasks, the physician's assistant would leave him more time to concentrate on those patients and situations requiring his special skills. Pediatricians working with nurse practitioners report that this association "provides them with at least one-third more time than they formerly had for patient care, reading, attendance at meetings, and other purposes. . . . Both professionals gain and the net result is improved patient care, benefit to society by conservation of scarce manpower resources, and the development of the role of each health professional to its fullest."<sup>18</sup>

Some nurses may feel threatened by the establishment of a new type of health professional; but nursing is a profession concerned with direct patient care, and the nurse is most efficiently used as the physician's professional associate, rather than as his assistant. And finally, although there may be some initial resistance, it has been found that patients quickly establish rapport with the physician assistant or nurse practitioner, and actually feel more free to call with minor problems.

It will be some time before educational programs now being planned will begin to produce large numbers of physician assistants. In a recent survey of practicing physicians in Wisconsin, it was found

that, among respondents, "61 percent believed that assistants were needed, and 42 percent stated that they would use an assistant in their practice." It is obvious that a real need is felt by physicians, and that there will be openings for as many assistants as can be educated in the next several years.<sup>19</sup>

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# The Concept of Mainstream Medicine For All Californians

## Fifth Progress Report of Committee On Role of Medicine in Society

### PART III

*This Fifth Progress Report is being printed in three parts in CALIFORNIA MEDICINE. Following the appearance of Part III the report will be bound in a pamphlet which may be ordered at \$1 a copy from 693 Sutter Publications, Inc., 693 Sutter Street, San Francisco, California 94102.*

IN PARTS I AND II of this report the Committee examined the history of the mainstream concept in health care as it has developed within the CMA and in California, certain assumptions which it seems reasonable to make for further planning, what the pluralistic approach is accomplishing in health care today, and some of the principal existing barriers to mainstream care for all Californians. Also the Committee identified a number of subject areas which appear to be in urgent need of study and development as essential to achieving the goal of "mainstream medicine for all Californians." In Part III the Committee suggests the broad outlines of what might be a comprehensive program for organized medicine in California to achieve this goal through its leadership. This will be considered in a number of categories of professional function as follows:

- The practicing physician
- The local or community medical society
- The regional approach
- The state medical association
- Annual California Congress on the State of Health Care

### The Practicing Physician

If the basic assumptions in Part I are correct, as appears likely, and particularly if the shortage of physicians is to be "permanent" as also appears likely, then the present role of the practicing physician will change. Further, if one considers that a license to practice granted by society through the state confers a privilege which is accompanied by a responsibility to society, then the licensee has some responsibility to adjust his practice to meet the needs of society, just as is the case with the licensed driver of an automobile on the highway. The concept of mainstream medicine for all Californians is an answer to a new determination of need by society, and it will require thoughtful reassessment and considerable modification of the "driving habits" of many California physicians if the goal is to be achieved.

The scope and responsibilities of medicine in today's society have been examined elsewhere.\* They are enormous, while physician manpower is quite limited, as is the productivity of any single physician. If the task is to be accomplished and the responsibilities met then ways must be found

Committee on Role of Medicine in Society: Burt L. Davis, John B. Dillon, Sanford Feldman, Elmer F. Goebel, John T. Saito, Marvin J. Shapiro, Malcolm C. Todd and Malcolm S. M. Watts, chairman; and, ex-officio, Henry V. Eastman and E. Kash Rose.

Parts I and II of this report appeared in the February and March, 1970, issues of CALIFORNIA MEDICINE.

\*Scope and Responsibility of Medicine. Calif Med 108:405-411, 1968, and 109:50-52; 168-171; 238-239; 332-333, 413-415, and 509-514, 1968



to extend the reach and effectiveness of the practicing physician substantially.

The Committee suggests that the finiteness of a physician's time is the principal limiting factor but that for physicians to work more hours is not the solution. The average is already approximately 60 hours a week. And the problem is not lessened by the fact that the requirements of many present day health care programs make many new demands upon the practicing physician's time and reduce his efficiency in many ways, as does the growing expectation that he will perform an increasing amount of professional and community service and provide visible and measurable evidence that he continues his education.

The Committee believes that if the professional commitment to the goal of mainstream medicine for all Californians is a serious one, the time is now at hand when each practicing physician will need to review his "driving habits" with a view to improving his productivity, extending his reach, providing time for his continuing education, professional and community service, and even his rest and recreation, since without this he cannot perform efficiently. For many this will entail new arrangements for practice with closer association with colleagues, greater use of human and mechanical aids, new ways of personalizing health care (perhaps through the use of assistants or associates from closely allied professions) and, to employ a current and overworked phrase, his education and continuing education will need to be more "relevant" to these areas of responsibility in practice.

*The Committee recommends that practicing physicians be encouraged to review their methods of practice; and in collaboration with others seek to extend their productivity and reach, and that incentives be developed for them to accomplish this within the framework of mainstream medicine.*

### The Local Medical Society

The county medical society, through its leadership and its membership, is the instrument through which the medical profession interfaces with the community. It parallels a basic political organization of society which is an advantage, but in many parts of California these political jurisdictions do not coincide with the natural social or economic boundaries and this may be a disadvantage in health care. However this may be, the present public acceptance and even promotion of

the concept that health is a community affair places great responsibility upon the local medical society and its membership if the medical profession is to provide effective leadership in the overall effort to achieve the goal of mainstream medicine for all Californians.

The Committee recognizes that many county medical societies in California have already and for a long time made major and innovative contributions toward the betterment of health care in their communities and for this they are to be commended. The Committee believes that what is needed now is a greater recognition by *all* local medical societies of a responsibility to assume leadership in their communities to find local solutions to local problems in health care and not to rest until this has been accomplished. It is no longer sufficient for a local medical society to wait for a community to ask it for advice, rather the local medical society should seek the help of its members and of the local community to make whatever innovations and adjustments are necessary to achieve the national purpose which is to provide equal access for all citizens to one-class, one-door, high quality medical care, without discrimination on the basis of race, creed, color or economic circumstances, yet with a maximum amount of local option and local control. The medical profession has always favored local as opposed to central control, and it is now necessary to prove that the national purpose in health care can be achieved through primary action at the local level.

*The Committee recommends that each local medical society be encouraged to recognize its primary and inescapable responsibility to assume professional and community leadership to bring about satisfactory local solutions to any barriers to "mainstream medicine for all Californians" which may be found to exist within the local jurisdiction.*

### The Regional Approach

In the previous section it was suggested that the county may not always be the best jurisdiction from the standpoint of function. For some functional purposes it may be too small and for others too large. Where it is too large the necessary geographical or functional subdivisions may be accomplished within a county medical society, but where it is too small the desirable regional arrangements have been far more difficult to achieve.

The Committee believes the time has come when regional groupings or associations of county

medical societies should be considered and probably developed in certain areas of the state. The evidence is that many aspects of health care financing and the organization of health care delivery will be planned and operated on a regional basis for reasons of both efficiency and economy. The further development of Comprehensive Health Planning (P. L. 89-749 as amended) will place additional emphasis on regional organization. For these reasons it would seem that strong organizational instruments of the CMA will be needed in a number of regions throughout the state to match regional organization in both the public and private sector if organized medicine is to play the significant leadership role it should in the development of mainstream medicine for all Californians.

*The Committee recommends that the CMA examine the possibilities of developing regional organizations within its structure which will provide an effective means of coordinating professional activity and exercising professional leadership for the betterment of health care in those regions of the state where this is being done on a regional basis.*

## The State Medical Association

The Committee finds that the State of California is a natural and functional entity not only from the geographical but also from the social, political and economic point of view. Conveniently its size is about one-tenth that of the United States. Largely for these reasons and because of the very rapid growth of the state in both population and productivity, with all the problems which these have created, the California Medical Association finds itself with a substantial experience in dealing with health care problems within these natural and functional boundaries, be the problems geographical, social, economic or political in nature.

The Committee believes that the CMA should now build upon this experience, develop further its knowledge and expertise, and through its leadership and organizational activity cause the necessary steps to be taken within and without the profession to make mainstream medicine for all Californians a reality.

Just as the local medical societies, and any regional medical organizations which may come into being, have a primary responsibility for finding local solutions to local health care problems, the state medical association has a primary responsibility to see that the mainstream requirements of

equality of access and equality of quality are also met statewide. The Committee believes that there are well established techniques by which this may be accomplished through voluntary means by the use of such things as "guidelines," "essentials," "certification," "accreditation" and the like. The Committee also believes that it should be the responsibility of the CMA to further develop and use these techniques, which as they come into being will, when taken together, constitute a framework for mainstream medicine in California.

The leadership role of the CMA is therefore a major one. It should be an instigator, advisor, coordinator, arbiter and advocate for mainstream medicine for all Californians. It should develop and refine the essentials for leadership discussed in Part II of this report and create the necessary guidelines to provide such a statewide framework for mainstream medicine. It should be a central information center, a communications center, an instrument of advocacy for the betterment of health care throughout the state, and a source of continuing public information with respect to the unsolved problems and the progress which has been made.

*The Committee recommends that the California Medical Association assume responsibility for exercising the leadership which will be needed, both within and without the profession, to make "mainstream medicine for all Californians" more nearly a reality in the state and a model for the nation.*

## An Annual Congress on California's Health

At the beginning of this report it was stated that the "mainstream" concept is voluntary and cooperative in emphasis, that it relies more on motivation than compulsion, that it is responsive to individual and local needs, and is dedicated to ensuring equal access to a single level of high quality health services and portability of protection in health care. Clearly if the goal of mainstream medicine for all Californians is to be achieved or even approached, there must be a cooperative effort within what is coming to be called the "health care industry," which is a loose term referring to the aggregate of many essentially autonomous components whose activities and goals may bear more or less of a relationship to one another. The Committee believes that there will be needed some mechanism or device which will act to orient and coordinate these properly autonomous and



pluralistic interests and activities for the betterment of health care.

It would seem that an annual congress on the state of health care in California in which all the parties at interest throughout the state would be invited to participate, could accomplish this purpose admirably, by identifying problems, setting goals and measuring the progress which is made each year. Since the medical profession is involved in one way or another in almost every aspect of the mainstream medicine for all Californians it would seem to be the most appropriate body in the private sector to act as convenor of such an annual congress.

*The Committee recommends that the California Medical Association assume the initiative in convening an "Annual Congress on California Health" of all the parties at interest in health care for the purpose of identifying problems, setting goals and measuring the progress which is made each year.*

## CONCLUSION

This *Fifth Progress Report* of the Committee on the Role of Medicine in Society assumes that mainstream medicine for all citizens is the national purpose in health care and that "Mainstream Medicine for All Californians" is a goal of the California Medical Association. The report seeks to outline in broad perspective some of the problems which exist and some of the steps to be taken to adapt mainstream care to the needs of today and tomorrow. The report is a call to action since in a very real sense the voluntary free enterprise system is on test to see whether or not it can provide mainstream medicine for all Californians.

## RECOMMENDATIONS

The Committee recommends that:

- *The Council undertake a "crash" program of study and research to develop an improved technology for health teams, centralization and decentralization of health services, health care plans and financing of health care, cost benefit assessment, leadership techniques and appropriate guidelines in each of these and other appropriate areas, which when taken together might constitute a kind of flexible framework for "mainstream medicine for all Californians."*
- *Practicing physicians be encouraged to review their methods of practice; and in collaboration with others seek to extend their productivity and reach, and that incentives be developed for them to accomplish this*

*within the framework of mainstream medicine.*

- *Each local medical society be encouraged to recognize its primary and inescapable responsibility to assume professional and community leadership to bring about satisfactory local solutions to any barriers to "mainstream medicine for all Californians" which may be found to exist within the local jurisdiction.*

- *The CMA examine the possibilities of developing regional organizations within its structure which will provide an effective means of coordinating professional activity and exercising professional leadership for the betterment of health care in those regions of the state where this is being done on a regional basis.*

- *The CMA assume responsibility for exercising the leadership which will be needed, both within and without the profession, to make "mainstream medicine for all Californians" more nearly a reality in the state and a model for the nation.*

- *The CMA assume the initiative in convening an "Annual Congress on California Health" of all the parties at interest in health care for the purpose of identifying problems, setting goals and measuring the progress which is made each year.*

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"Mainstream"—one level, high quality, economically efficient, equally accessible to all.

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# LETTERS *to the Editor*

## Medical School Graduates For Patient Care

*To the Editor:* It has recently been brought to my attention that many persons believe that graduates of California medical schools are encouraged to devote their careers to research rather than to patient care. In view of the concern over the shortage of practicing physicians and other health professionals, I would like to set forth the facts of the matter.

According to a report on medical school alumni published by the American Medical Association in 1968, nearly 90 percent of all medical school graduates in the country were engaged in patient care as their major professional activity, almost 4 percent were medical school faculty, 1.4 percent were administrators, and 1.5 percent were engaged in research. The figures for the University of California are nearly identical: slightly over 90 percent of our graduates are in practice while only 1.5 percent are researchers.

We at the University of California are proud of the role our graduates are playing in serving the people of the state, and we look forward to an even greater contribution as our new schools at Davis, Irvine, and San Diego mature.

CHARLES J. HITCH, LL.D.  
*President*  
*University of California*

*EDITOR'S NOTE: President Hitch's letter should serve to overcome a misconception that might diminish the needed "Yes" vote on Proposition 1—The Health Sciences Construction Bonds. The Council of the California Medical Association has endorsed Proposition 1 which is to be voted upon June 2, 1970, and urges every member of the Association to actively support it.*

## A Medical Student Responds to a Question

*To the Editor:* There is no question that the California Medical Association can make a significant contribution to the problem of overpopulation in the United States. Certainly it would be useful to establish study groups so that physicians can better educate themselves, and, hopefully, educate their patients as well. But far more important a contribution, it seems to me, would be for the CMA to go on record strongly disapproving anyone, physicians included, having more than two children.

Many physicians feel that they can easily afford more than two children and, furthermore, their children are likely to be well-educated and make contributions to the welfare of society. As a result many physicians feel that though there is a "population explosion" they themselves are personally exempt from responsibility for it. It is precisely this attitude that must be examined, and examined closely. A physician's child, like any other American child, is a master-consumer, and during his or her lifetime more of a threat to the world's irreplaceable and diminishing resources than an

entire village in India. When we think of our future the by-now familiar specter of ever-increasing smog, pollution, and horrendous freeway crowding arises before us. In addition, the amoeba-like, cancerous sprawl of urban developments inexorably paving over peri-urban greenery makes clear the necessity, beginning now, of no exceptions to the moral imperative of the two-child limit.

Physicians are an influential component of the opinion-making elite in California. Now that thousands of doctors have quit smoking and urged their patients to do the same, we are beginning to see results. When doctors start refusing to have more than two children, and urge their patients to do the same, their impact may be profound. To do less would clearly be abrogating the physician's responsibility to maintain the highest level of health in the community. It is to this end that I feel the CMA should direct its efforts.

STEVEN SOLTER

*Senior Medical Student,  
Stanford University School of Medicine*

## MEDEX Program

*To the Editor:* Having spent two years in a general practice residency and five years in private general practice, I am very much aware of the need to supplement the physician's time and energy with qualified and trained individuals to do many of the things which the physician himself is now forced to do. I have been following with interest the developments at Duke and the University of Colorado with their training of physician's assistants. The most recent program in this area, the MEDEX program at the University of Washington, seems to be an excellent new approach, not only filling the need, but also utilizing personnel who otherwise would find little or no use for their abilities in civilian life; and additionally, not depriving other professions (such as public health nurses) of badly needed people. I note with interest that the Washington State Medical Association is a co-sponsor of the MEDEX program, and would strongly encourage the CMA to begin immediately to investigate and implement the same type of, or similar, program.

In short, the private physicians, especially in rural areas, are being swamped, and we need help.

We can't wait for new M.D.'s, and in many instances we don't need such highly trained personnel. We need capable people in intermediate positions, and the sooner the state association realizes this and starts advancing in this direction, the sooner the people in California, including its doctors, will have adequate medical care.

N. B. SMITH, M.D.

*Woodland*

## More Nutrition

*To the Editor:* Dr. Tom Brewer has kindly sent me a copy of his letter to the editor of CALIFORNIA MEDICINE [published in the March, 1970, issue]. This letter concerns the December, 1969, White House Conference on Food, Nutrition and Health. The letter presents several statements and points of view which, if taken by themselves, might create too restrictive a view of the purposes and accomplishments of the Conference. In this connection, the final report of the Conference will be published in March, 1970. I believe that the study of the final report will be well worth the time involved. As Dr. Mayer stated in his letter of transmittal, "The demonstration that, at a time when divisions and confrontations are common in our land, forceful and sometimes militant Americans of all walks of life and persuasion can be brought together and, after spirited discussion, agree on common priorities in the service of the Country and of one's fellow man is deeply reassuring."

Nevertheless, one point made in the letter does require emphasis. As the letter properly states, "one urgent need is *to apply* (author's italics) scientific nutrition in human prenatal care." This statement in turn leads to questions about how this should be done, under what circumstance, who should do it, where should the responsibility lie, and so on. And, it was precisely to questions such as these that the work of the Conference was addressed, as can be seen in its report.

HOWARD N. JACOBSON, M.D.

*Harvard University Medical School  
Formerly Vice-Chairman, Panel on  
"Establishing Guidelines for the Nutrition  
of Vulnerable Groups (With Special  
Reference to People with Inadequate Food  
Budgets); Pregnant and Nursing Women and  
Infants." White House Conference on  
Food, Nutrition and Health*

# Etiology and Pathogenesis Of Hypertension

HARRIET P. DUSTAN, M.D.

*Material Supplied by the California Heart Association*

HYPERTENSION is a major cardiovascular problem that is largely unsolved. However, there are a variety of drugs available for treatment which used singly or in combination reduce arterial pressure substantially. Such therapeutic effectiveness tends to obscure the fact that we actually know very little about the mechanisms of hypertension and the functional details of its natural history.

Hypertension is a symptom, not a disease. We know it to be associated with a variety of diseases, but these affect only a small number of patients so that in most hypertension is without apparent cause. This condition is called essential hypertension. The term is an archaic misnomer because we know that hypertension is not essential for anything. Long gone are the days when physicians believed elevated arterial pressure to be essential for maintenance of tissue perfusion.

Although elevated blood pressure, of itself, is a symptom, it is often associated with vascular diseases—arteriolar sclerosis or premature atherosclerosis. Arteriolar disease occurs more commonly in patients with severe diastolic hypertension, while premature atherosclerosis is usually a manifestation of long sustained arterial pressure elevation, even one of mild degree.

Hypertension can be classified in a number of ways according to: (1) the type of arterial pressure elevation—systolic, diastolic, or mixed, (2) the character of the elevation—labile or sustained, (3) severity of the associated vascular disease—mild, moderate, severe, or malignant (accelerated), (4) or etiology—renal, adrenal, cardiovascular, or essential. At our present level of knowledge, the etiologic classification is the most interesting. Not only does recognition of the various causes of elevated arterial pressure lead to more rational

treatment, but also it gives an opportunity to study the mechanisms of hypertension.

The hypertensions that are associated with various diseases are called secondary. When none of these conditions is present, the hypertension is said to be primary. This term, like "essential," is a misnomer because each hypertension has a cause even though our knowledge is not sufficient to recognize it. Clearly, the more we have learned the more we have seen; for example, consider the types of hypertension recognized in the past 20 years. These include primary aldosteronism, renal arterial disease, and increased activity of the beta-adrenergic component of the sympathetic nervous system. Before these types were recognized, such patients were considered to have "essential" or "primary" hypertension.

The physiologic abnormalities that have been found in hypertensives relate to the nervous control of the circulation, catecholamines, cardiac output and peripheral resistance, adrenal steroids, the renal pressor system and plasma volume. Evidence is accumulating that these factors do not operate alone, and it seems likely that they make up an integrated system, one expression of which is elevated blood pressure.

When considering the etiology and pathogenesis of hypertension, it is an interesting exercise to see how these various factors are interrelated in the different types of hypertension. Of course, our present information is incomplete, but enough is available to make the exercise worthwhile.

The most frequently occurring secondary hypertensions now recognized are those associated with renal arterial disease and renal parenchymal disease, pheochromocytoma, primary aldosteronism, coarctation of the aorta and increased activity of the beta-adrenergic nervous system.

In patients with renal arterial disease, the most likely cause of hypertension is, of course, the renin-angiotensin system. However, elevations of renin (which is the component most readily measured) are not routinely found. This suggests that other factors are also operating and since blood pressure can be lowered with drugs that suppress the activity of the sympathetic nervous system, this indicates a nervous component in the hypertension as well. In fact, we have recently shown that these patients often have exaggerated increases in blood pressure in response to head-up tilt. Further, they tend to have slightly increased cardiac output which may represent an increase in nervous stimulation

Dr. Dustan is from the Research Division, Cleveland Clinic, Cleveland, Ohio.



of the heart. Plasma volume can be decreased and, in our experience, it is inversely related to the plasma renin activity. Additionally, aldosterone production is often increased producing a state of secondary aldosteronism. Thus, although we cannot put together all the pieces of information in an integrated fashion, evidence is accumulating that the hypertension accompanying renal arterial disease is an expression of a variety of abnormalities, only one of which is a disturbance of the renin-angiotensin system.

In renal parenchymal disease, there is not so much information available concerning the possible pressor factors. However, there have been studies in patients with chronic renal failure which show expansion of the extracellular fluid volumes and correction of hypertension when these excesses are corrected by dialysis. Further, there is a suggestion that with expanded plasma volume the nervous control of the circulation is lessened—possibly because it isn't so necessary when the blood volume is high. Plasma renin activity has not been consistently found to be elevated although increased activity of the renin-angiotensin system seems likely in patients whose hypertension remits following bilateral nephrectomy done in preparation for transplantation. Thus, in this type of hypertension, there are indications that, in one way or another, three pressor factors participate—renal pressor, neurogenic, and fluid volume.

Pheochromocytoma seems a much more straightforward problem than that presented by the other two types of hypertension. Currently, we know that there is increased epinephrine and norepinephrine production, and this seems reason enough for the hypertension. Plasma volume can also be reduced, and this is important because it may explain the

hypotensive crises that often occur in these patients following surgical removal of the tumor.

In primary aldosteronism, there is an increased production of aldosterone which can cause increases in body sodium, extracellular fluid volume and plasma volume. Along with these increases, decreased activity of the sympathetic nervous system has been reported. Plasma renin activity is low, suggesting that this is not a factor in the hypertension.

Increased activity of the beta-adrenergic component of the sympathetic nervous system can be associated with hypertension. These patients have palpitations and exaggerated tachycardia in response to a variety of normal stimuli, such as exercise. They have increased cardiac output but a normal or near normal peripheral resistance. Their hypertension can be controlled with beta-blocking drugs such as propranolol.

Coarctation of the aorta is also recognized as occasional cause of hypertension. If patients are not in cardiac failure, apparently hemodynamic functions are normal, at least in the upper parts of the body above the coarctation. However, until flow beyond the coarctation can be measured reliably, hemodynamic characteristics of this type of hypertension cannot be determined. Other pressor mechanisms have not been studied in such patients.

Although most treatments of hypertension are empiric rather than based on specific pressor mechanisms, information is becoming increasingly available in various types of hypertension which bids well to describe a number of integrated circulatory disturbances, of which hypertension is one manifestation. These descriptions will provide rational, rather than empiric, treatment.

# PUBLIC HEALTH REPORT

Louis F. Saylor, M.D., M.P.H., Director, State Department of Public Health

## Pesticides and Public Health

THE STATE DEPARTMENT of Public Health is co-operating with the University of California under legislative mandate to collect and collate pertinent scientific data on the effects of DDT and similar insecticides and pesticides. The department recently reported to the legislature on pesticide-related public health and environmental problems.

Considerable attention has been focused on the content of chlorinated hydrocarbons pesticides in human adipose tissues. DDT-derived materials are found in almost all samples of human adipose tissue analyzed. A limited number of observations show that DDT levels in the tissue of Alameda County residents approximate those of Chicago, Illinois, residents. Levels in Kern County are higher than those in Alameda County, even when agricultural workers are excluded from the comparison. Both in California and elsewhere Negroes have higher levels than Caucasians. A sex difference is often reported, with the male showing higher levels than the female in studies of Caucasians and Negroes in Alameda County and Chicago. Age has little effect on the levels. We do not know what significance these findings have in human illness.

Much concern has been aroused by the fact that levels of DDT-derived materials in the milk of many mothers exceed the tolerance set by the Federal Food and Drug Administration for cow's milk. Nationwide studies indicate that the level in human milk ranges from 0.05 to 0.37 parts per million (ppm), probably averaging about 0.1 to 0.2 ppm. FDA tolerance for DDT-derived materials in cow's milk has been established at 0.05 ppm. The average breast-fed child ingests daily about 0.02 mg DDT-derived materials per kilogram of body weight, twice the "acceptable daily intake" recommended by the World Health Organization. Again, what risk this constitutes to the nursing infant is unknown.

It has been estimated that about one-half of the body burden of DDT comes from home use of DDT. The other half is contributed by dietary, airborne and waterborne exposures to pesticides but in such

small quantities that they do not represent a serious threat to the general population of California.

Injuries and accidental poisonings constitute actual and potential hazards. Despite tight restrictions on purchase of pesticides for home use, some children are injured each year as a result of improper handling or careless storage of pesticides in the home, ranging from arsenic in past years to the chlorinated hydrocarbons more recently. A few accidents have occurred in California during transportation and storage of the highly toxic organophosphates. They involved highway spills and contamination of clothing and food. These are continuing dangers with a potential for injuring many persons at once. A grave threat potentially exists in improper disposal of used pesticide containers in unsupervised dumps and elsewhere. The State Department of Public Health is developing a comprehensive study of this problem and will recommend a pesticide container management system.

The population at greatest risk of pesticide poisoning consists of agricultural and occupational groups. Since 1950 the department has published annual statistical reports of occupational disease attributed to agricultural chemicals. In the past decade the number of reports received each year has not changed significantly, except for two outbreaks of parathion poisoning among agricultural workers in 1959 and 1963. Occupational illness may be under-reported, however, at least so far as organophosphate pesticides such as parathion are concerned. The department will test this hypothesis in a study based on laboratory evidence, involving levels of the enzyme cholinesterase, a highly reliable indicator of recent exposure to organophosphate pesticides.

The widespread effects of pesticides on the environment constitute another problem of great public concern. In addition to general contamination of the environment, pesticide pollution causes wildlife losses among fish and birds. DDT and other persistent pesticides also produce subtle effects through animal food chains, undergoing increasing concentration as they pass from lower to higher organism. The consequences of this food chain magnification are not completely understood, but

recent declines in populations of carnivorous birds have been attributed to accumulation of DDT and its metabolites in bird tissues and eggs. In addition, DDT may build up to levels higher than the 5 ppm tolerance set for edible fish and game. Four thousand cartons of tinned mackerel were withheld from the market for this reason.

Recently the California Director of Agriculture directed that DDT and the related pesticide DDD be eliminated from all present uses within two years. This is one of a long series of laws and regulations on pesticides developed by the California Department of Agriculture since 1927.

The elimination of DDT and DDD requires that an orderly and scientific procedure be followed to cause the least amount of disruption to agricultural production and the environment. In some instances, the substitution of less persistent but more toxic pesticides, such as the organophosphates, for DDT in insect control has upset the agro-ecosystem. Present substitutes for DDT have a broad spectrum of activity and a short residual effect. They kill beneficial predators and parasites and the pest species then return in greater numbers than before treatment because there are no natural controls. If DDT is used where possible for one more season,

a complete transition can probably be made to some of the other compounds without seriously disrupting crop production or the local agro-ecosystem. However, the greater toxicity of the organophosphates may cause an increase in the incidence of occupational and home pesticide morbidity.

Both the federal and the state legislatures passed significant pesticide legislation in 1969. California laws strengthen regulation and control of pesticide use and sale. They provide for the examination and licensing of dealers and give the Director of Agriculture added powers to register and cancel the registration of pesticides. In addition, recent legislation calls for the appointment of an advisory committee to the director to help him establish criteria and regulations for the prevention of damage to California's environment.

Pesticides play a vital role in eradicating disease-bearing vectors and in producing high grade food. The State Department of Public Health with other appropriate agencies will continue to conduct surveillance and epidemiological studies on the acute poisoning and long-term health hazards of pesticides, as well as their effects on environmental quality.

## AMENORRHEA AND ORAL CONTRACEPTIVES

"As far as is known, no one can tell which patients who will have amenorrhea following oral contraceptive drugs, with one possible exception. It has been repeatedly shown that patients who have irregular menses or who have periods of stress amenorrhea are almost invariably made worse by oral contraceptives. It's our policy to first warn patients of this type that amenorrhea and infertility might occur for a period after cessation of oral contraceptives. If they still want the pills, then we feel that the sequential should be prescribed."

—ROBERT R. FRANKLIN, M.D., Houston

Extracted from *Audio-Digest Obstetrics and Gynecology*, Vol. 16, No. 2, in the Audio-Digest Foundation's subscription series of tape-recorded programs.



# California Medical Association



## Council Highlights

### Highlights of the Actions of the California Medical Association Council Meeting, January 9 to 10, Los Angeles

*This summary is published so that CMA membership may be advised in brief of the actions of the Association's Council. It covers only major actions and is not intended as a detailed report. Full minutes of these meetings are available upon any member's request to the CMA office.*

#### 560th Meeting, January 9 to 10, 1970 Los Angeles

**A Professional Liability Legislative Program For 1970** was approved. The liability package, with eight recommendations, includes two bills on measure of damages. One of the most far-reaching proposals in the liability package calls for a study on possible development of an association made up of insurance companies writing liability coverage in California. This association would be required to make professional liability insurance available.

**A \$20 dues increase** was recommended in order to provide funds for new activities to put CMA in a leadership role in the health care field during the 1970s as well as compensating for the rise in operating costs facing the Association due to inflation. CMA dues have remained at the same level for the past four years. The recommendation will be submitted to the House of Delegates next March.

**Council assigned the Commission on Allied Health Professions and Services** to study the

training, education and responsibilities of the assistant to the physician.

**A draft of "Guiding Principles for Long-Term Care in Nursing Homes"** was approved. It will be submitted to the CMA House of Delegates for ratification.

**Merger of the CMA Committee on Health Care for the Aging with the CMA Committee on Long-Term Care Facilities** was approved. The combined committee was renamed "Long-Term Care Survey Committee." Creation of the new committee is an important step in extending the CMA survey concept to long-term care facilities.

**The CMA Investment Policy and Procedural Manual**, which provides guidelines for management of the CMA investment reserve fund, was adopted.

CMA support of the Health Science Facilities Construction Bond Issue (Proposition 1) was pledged by Council. A motion also was approved calling for a \$25,000 contribution and a public information campaign.

# New CMA Officers



DR. RALPH W. BURNETT



DR. ROBERTA F. FENLON

DR. RALPH W. BURNETT of Bakersfield was installed as president of the California Medical Association at the annual meeting, March 7-11, in San Francisco. He succeeded Dr. Albert G. Miller of San Mateo. Dr. Roberta F. Fenlon of San Francisco was elected president-elect, the first woman ever named to that post.

Dr. William F. Quinn and Dr. Joseph F. Boyle of Los Angeles were reelected speaker and vice-speaker, respectively, of the House of Delegates.

The new president, who is in general practice, received his MD from Loma Linda University. He is past chairman of the Department of Internal Medicine of the Kern County General Hospital, past president of the Greater Bakersfield Memorial Hospital staff, guest lecturer at Bakersfield College, trustee of the Kern County Foundation for Medical Care, a trustee of California Blue Shield, and a past president of Kern County Medical Society. Dr. Burnett has served on many CMA committees.

Dr. Fenlon, a graduate of the University of Iowa School of Medicine, is an internist in private practice in San Francisco and is a clinical professor of medicine at the University of California, San Francisco Medical Center. In 1965, soon after the passage of Medicare, she relinquished her practice for several months to serve as consultant to the director of the Bureau of Health Insurance of the Social Security Administration on means to implement the legislation. Dr. Fenlon has been a member of the CMA Council for six years, is vice chairman of California Blue Shield's Board of Trustees and a past president of the San Francisco Medical Society. She also is a director of the Florence Crittenton Home in San Francisco, a governor of the San Francisco Heart Association and medical director of Visiting Nurses Association.

Three new members were elected to the CMA Council. They are Drs. Ralph M. Milliken, Los Angeles; Harry J. Fryer, Jr., San Luis Obispo; and Sanford E. Feldman, San Francisco.

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## In Memoriam

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ROBERT ALWAY PEERS, M.D.  
1875-1970

ROBERT ALWAY PEERS, M.D., a pioneer in tuberculosis, died at his home in Palo Alto on February 7, 1970. He was 94. He was a native of Woodstock, Ontario, and was graduated from Trinity Medical College, Toronto, with the degree of M.D.C.M. in 1899.

In the English tradition and custom of that time, Dr. Peers purchased a practice, that of a physician in Colfax, California, and entered general practice in 1899. These were horse-and-buggy days. Dr. Peers was a vigorous young man and this author, his close friend and admirer, enjoyed listening to stories of the ardors of practice in the snow in the Sierra Nevadas. He was a humanitarian, and his fees were always in proportion to his patient's circumstances.

He became a naturalized citizen in 1904. In 1908 he founded the Colfax School for the Tuberculous, served as its medical director until 1941, and remained as a consultant until his retirement in 1946. Many physicians "took the cure" there. Some stayed for several years under his tutelage and then left to become prominent locally, nationally and internationally as specialists in diag-

nosis, treatment and research in diseases of the pulmonary system. He was widely honored in this field, and in others as well, where his accomplishments were many.

During World War I, Dr. Peers served as a captain in the American Red Cross and had seven hospitals in the south of France under his jurisdiction. He was a member of the California State Board of Public Health from 1914 to 1941.

He was president of the California Medical Association in 1936 and among his medical honors was the first Certificate of Merit granted by the California Medical Association, and a 50-year pin marking half a century of membership in the association. He served in the House of Delegates of the American Medical Association 1937-1944 and was a member of the Board of Trustees in 1945.

Dr. Peers was Mayor of Colfax for 23 years and was twice a delegate to the Republican National Convention.

To his younger colleagues and friends, Dr. Peers was always referred to in conversation respectfully as "The Doctor" in the connotation of all that was fine in the traditions of our profession.

RAY C. ATKINSON, M.D.  
*Oakland*

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ANDERSON, MILFORD XERXES, Corona del Mar. Died February 17, 1970 in Los Angeles of malignant disease, aged 63. Graduate of Northwestern University Medical School, Chicago, 1933. Licensed in California in 1933. Doctor Anderson was a member of the Orange County Medical Association.

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BRUFF, WILLIAM CORTLAND, Whittier. Died January 24, 1970 in Whittier of heart disease, aged 73. Graduate of Rush Medical College, Chicago, 1922. Licensed in California in 1925. Doctor Bruff was a member of the Los Angeles County Medical Association.

Persons wishing to do so may make contributions to the Physicians' Benevolence Fund to honor the memory of a member who has died. Members of the family will be notified that such a contribution has been made and the name of the donor will be supplied.

Checks should be addressed to Physicians' Benevolence Fund, Inc., California Medical Association, 693 Sutter Street, San Francisco, Ca. 94102.



FISKIN, ROBERT DEAN, Altadena. Died February 19, 1970 in Pasadena of pulmonary embolism, aged 38. Graduate of University of Southern California School of Medicine, Los Angeles, 1957. Licensed in California in 1958. Doctor Fiskin was a member of the Los Angeles County Medical Association.



GOODMAN, ROBERT HERMAN, Woodland Hills. Died February 7, 1970 in Canoga Park of coronary artery disease, aged 42. Graduate of Tulane University School of Medicine, New Orleans, 1950. Licensed in California in 1951. Doctor Goodman was a member of the Los Angeles County Medical Association.



KUNTZ, JAMES F., Folsom. Died February 15, 1970 near Placerville in a light plane crash, aged 35. Graduate of Indiana University School of Medicine, Bloomington-Indianapolis, 1962. Licensed in California in 1963. Doctor Kuntz was a member of the Sacramento County Medical Society.



MADLEM, LEO S., JR., Claremont. Died February 3, 1970 in Pomona, aged 54. Graduate of Stanford University School of Medicine, Palo Alto-San Francisco, 1942. Licensed in California in 1942. Doctor Madlem was a member of the Los Angeles County Medical Association.



NEUGEBAUER, WILLIAM FAY, Pasadena. Died November 23, 1969 in Pasadena of heart disease, aged 70. Graduate of the College of Osteopathic Physicians and Surgeons, Los Angeles, 1926. Licensed in California in 1926. M.D. degree from California College of Medicine, 1962. Doctor Neugebauer was a member of the Los Angeles County Medical Association.



PEERS, ROBERT ALWAY, Palo Alto. A past-president of the California Medical Association died February 7, 1970 in Palo Alto, aged 94. Graduate of Trinity Medical College, Toronto, Canada, 1899. Licensed in California in 1899. Doctor Peers was a member of the Placer-Nevada County Medical Society, a life member of the California Medical Association, and a member of the American Medical Association.



REDDIN, ROBERT LEE, Santa Barbara. Died February 4, 1970 in Santa Barbara of injuries received when his dune

buggy overturned, aged 46. Graduate of the University of Oklahoma School of Medicine, Oklahoma City, 1955. Licensed in California in 1957. Doctor Reddin was a member of the Santa Barbara County Medical Society.



ROGERS, HOBART, Oakland. Died February 19, 1970 in Oakland of cerebral infarction due to cerebral arteriosclerosis, aged 72. Graduate of Indiana University School of Medicine, Bloomington-Indianapolis, 1922. Licensed in California in 1924. Doctors Rogers was a retired member of the Almaeda-Contra Costa Medical Association and the California Medical Association, and an associate member of the American Medical Association.



ROTHMANN, HANS, San Francisco. Died February 28, 1970 in San Francisco, aged 70. Graduate of Friedrich-Wilhelms-Universität Medizinische Fakultät, Berlin, Prussia, 1924. Licensed in California in 1942. Doctor Rothmann was a member of the San Francisco Medical Society.



SHARP, KLENNER F., Fresno. Died January 24, 1970 in Fresno, aged 65. Graduate of Rush Medical College, Chicago, 1933. Licensed in California in 1934. Doctor Sharp was a member of the Fresno County Medical Society.



STECKLER, ROBERT J., Thousand Oaks. Died January 21, 1970 in Thousand Oaks of cancer of the pancreas, aged 47. Graduate of University of Maryland School of Medicine, Baltimore, 1949. Licensed in California in 1950. Doctor Steckler was a member of the Ventura County Medical Society.



STERNHILL, BERNARD, Malibu. Died February 24, 1970 in Los Angeles of acute coronary occlusion, aged 53. Graduate of the Creighton University School of Medicine, Omaha, 1942. Licensed in California in 1943. Doctor Sternhill was a member of the Los Angeles County Medical Association.



WELDEN, ROBERT C., Oceanside. Died February 27, 1970 in Oceanside, aged 57. Graduate of the University of Southern California School of Medicine, Los Angeles, 1938. Licensed in California in 1938. Doctor Welden was a member of the San Diego County Medical Society.

CMA REDWOOD REGIONAL CONFERENCE  
FOR NORTH COAST COUNTIES

*Konocti Harbor Inn, Clear Lake*  
*May 15-16, 1970*

**program:**

THE ANEMIC PATIENT

MUSCULO-SKELETAL DISORDERS

**presented cooperatively by**

North Coast Counties Medical Societies

University of California at San Francisco

California Medical Association

**host:** Mendocino-Lake Counties Medical Society  
Austin E. Givens, M.D., Regional Chairman

**guest speaker:** James H. Jandl, M.D., George Richard Minot  
Professor of Medicine, Harvard Medical School  
(made possible by a grant from Merck, Sharp &  
Dohme Postgraduate Program)

**contact:** For additional information write:  
Continuing Medical Education  
California Medical Association  
693 Sutter Street, San Francisco 94102

**fee:** \$20

All California Medical Association members and their families  
are cordially invited to attend.

# CONTINUING MEDICAL EDUCATION ACTIVITIES IN CALIFORNIA AND HAWAII

(FORMERLY WHAT GOES ON)

## COMMITTEE ON CONTINUING MEDICAL EDUCATION

THIS BULLETIN of information regarding continuing education programs and meetings of various medical organizations in California and Hawaii is supplied by the Committee on Continuing Medical Education of the California Medical Association. In order that they may be listed here, please send communications relating to your future meetings or postgraduate courses to Committee on Continuing Medical Education, California Medical Association, 693 Sutter Street, San Francisco 94102; or phone: (415) 776-9400, extension 241.

## ALCOHOLISM AND DRUG USE

May 16 & 23—**The Drug Scene.** University of California Extension, Riverside, at 1500 Life Sciences Building, UC Riverside. Two Saturdays. Primarily for physicians. 14 hrs. Contact: Ray Olitt, Health Services Program Coordinator, UC Extension, Riverside 92502. (714) 787-4329.

## CANCER

May 15-16 — **Hormones and Neoplasms—Cancer Conference.** USC at Century Plaza Hotel, Los Angeles. Friday-Saturday. Parathyroid neoplasms, adrenal neoplasms, thyroid neoplasms. 12 hrs.

## MEDICINE

April 17—**A Symposium Offering a Practical Approach to Office Diagnosis and Management of Respiratory Diseases.** Academy of General Practice, San Diego County Medical Society, Smoking Research/San Diego, Riker Laboratories at Town and Country Hotel Convention Center, San Diego. Friday. 6½ hrs. Contact: Worth Larkin, Public Relations Director, TB and Health Assoc. of San Diego and Imperial Counties, 3861 Front St., San Diego 92103. (714) 297-3901.

April 18—**Infectious Diseases.** UCSF at Childrens Hospital, San Francisco. Saturday. Infections Associated with Intravenous Catheters, with Inhalation RX, and with Urinary Catheters; Overview of Host Defense; Antibiotics—1970; Isolation Procedures. \$35. 5½ hrs.

April 22-25—**Advances in Endocrinology and Metabolism.** UCSF. Wednesday-Saturday. Intensive review of interrelationships between metabolic disease and endocrine dysfunction, critical evaluation of new developments.

May 4-15—**Coronary Care Unit Program for Physicians.** CRMP Area V at Los Angeles County-USC Medical Center. Two week course repeated monthly through June, 1970. Arrhythmia detection, diagnosis and therapy, defibrillation and cardioversion, central

venous pressure monitors, placement of pacing catheters, new aspects in diagnosis and treatment of congestive heart failure, shock and associated respiratory problems, and CCU management in community hospitals. Contact: Gladys Ancrum, Dr. P. H., Administrative Associate, CRMP Area V, 1 West Bay State St., Alhambra 91801. (213) 576-1626.

May 4-22—**Coronary Care for Physicians Training Program.** CRMP Area IV and Cedars-Sinai Medical Center at Cedars of Lebanon Hospital, Los Angeles. Three week course repeated six times through November, designed for practicing internists or cardiologists who will subsequently be working in or directing CCU in community hospitals. Electrocardiography, physical diagnosis, CCU planning and administration, electrolytes and acid-base metabolism, emphasis on practical techniques. Contact: Herbert Stein, M.D., Coronary Care for Physicians Training Programs, Dept. of Cardiology, Cedars of Lebanon Hospital, Box 54265, Los Angeles 90029. (213) 662-9111, ext. 306.

## KEY TO ABBREVIATIONS AND SYMBOLS

### Medical Centers and CMA Contacts for Information

- CMA:** California Medical Association  
Contact: Continuing Medical Education, California Medical Association, 693 Sutter Street, San Francisco 94102. (415) 776-9400, ext. 241.
- LLU:** Loma Linda University  
Contact: John E. Peterson, M.D., Associate Dean for Research Affairs, Loma Linda University School of Medicine, Loma Linda 92354. (714) 796-7311.
- PMC:** Pacific Medical Center  
Contact: Arthur Selzer, M.D., Chairman, Education Committee, Pacific Medical Center, Clay and Webster Streets, San Francisco 94115. (415) 931-8000.
- STAN:** Stanford University  
Contact: Thomas A. Gonda, M.D., Associate Dean, Stanford University School of Medicine, 300 Pasteur Drive, Stanford 94305. (415) 321-1200, ext. 5371.
- UCD:** University of California, Davis  
Contact: George H. Lowrey, M.D., Professor and Chairman, Department of Postgraduate Medicine, University of California, Davis, School of Medicine, Davis 95616. (916) 752-0331.
- UCI:** University of California—California College of Medicine, Irvine  
Contact: Robert Combs, M.D., Associate Dean, University of California, Irvine—California College of Medicine, Irvine 92664. (714) 833-5991.
- UCLA:** University of California, Los Angeles  
Contact: Donald Brayton, M.D., Associate Dean and Head, Continuing Education in Medicine and the Health Sciences, 15-39 Rehabilitation Center, UCLA Center for the Health Sciences, Los Angeles 90024. (213) 825-6514.
- UCSD:** University of California, San Diego  
Contact: Michael Shinkin, M.D., Associate Dean for Health Manpower, 1309 Basic Sciences Building, University of California, San Diego, School of Medicine, La Jolla 92038. (714) 453-2000, ext. 2704.
- USCF:** University of California, San Francisco  
Contact: Seymour M. Farber, M.D., Dean, Educational Services and Director, Continuing Education, Health Sciences, University of California Medical Center, San Francisco 94122. (415) 666-1632.
- USC:** University of Southern California  
Contact: Phil R. Manning, M.D., Associate Dean, Postgraduate Division, University of Southern California School of Medicine, 2025 Zonal Avenue, Los Angeles 90033. (213) 225-1511, ext. 203.



- May 9—**Symposium on Clinical Pharmacology and Drug Therapy.** Division of Clinical Pharmacology, Department of Medicine, STAN, and Palo Alto Medical Clinic at STAN. Saturday. \$15, no fee for medical students and house staff. Contact: Stanley N. Cohen, M.D., Room S-161, STAN. (415) 321-1200, ext. 6021.
- May 9—**Diseases of the Gastrointestinal Tract.** See Radiology—Pathology, May 9.
- May 12—**Analytical Approach to Cardiac Diagnosis.** American College of Cardiology and LLU at LLU. Tuesday. Representative cases of heart disease: history, examination, laboratory and radiological procedures. 7 hrs. Contact: William D. Nelligan, Exec. Dir., ACC, 9650 Rockville Pike, Bethesda, Md. 20014. (301) 530-1600.
- May 13-14—**Coronary Care.** USC at Hilton Hotel, Los Angeles. Wednesday-Thursday. 12 hrs.
- May 15—**California Heart Association—Annual Meeting Scientific Sessions.** Hotel del Coronado, Coronado. Friday. Coronary thrombosis and myocardial infarction, problems in ECG diagnosis of myocardial infarction, premature coronary disease, coronary arteriography. \$10. 7 hrs. Contact: Rodman D. Starke, M.D., 1370 Mission St., San Francisco 94103. (415) 626-0123.
- May 15 & 16—**Physical Signs in Cardiovascular Disease.** STAN, Santa Clara and San Mateo Heart Associations, and CRMP Area III at Palo Alto Veterans Administration Hospital, Palo Alto. Friday & Saturday. One day course repeated two successive days. Review of important physical signs of cardiovascular disease. A.M., examination of cardiac patients; P.M., systematic review of physiological basis and implications of salient physical signs. Contact: Herbert Hultgren, M.D., Medical Service (III), Palo Alto V.A. Hospital, 3801 Miranda Ave., Palo Alto 94306. (415) 326-5600.
- May 15-17—**Basic Principles of Cardiac Therapy.** PMC and the American College of Cardiology at Jack Tar Hotel, San Francisco. Friday-Sunday. Clarification of pathophysiological basis of various disease states, rational approach to drug usage. \$80 members, \$120 non-members. 24 hrs. Contact: PMC.
- May 16—**Progress and Problems in Neurology for the '70s.** Palo Alto Medical Clinic and Research Foundation, Palo Alto. Saturday. Treatable Forms of Dementia; Mechanisms of Developmental Defects of the Nervous System; New Concepts of "Degenerative" Neurological Diseases—The Role of Slow Viruses; The Medical and Neurological Implications of Space Travel; Recent Advances in Adult Neurology—Parkinsonism and DOPA; "Pot" and "Acid" — The Medical and Neurological Implications of the Drug Problem; The Current Status of Strokes and Anticoagulation; Senile Neuronal Drop-Out — The Problems of Growing Old Gracefully. \$15. 5½ hrs. Contact: Bernard I. Lewis, M.D., Palo Alto Medical Clinic and Research Foundation, 300 Homer Ave., Palo Alto 94301. (415) 321-4121.
- May 16-17—**Current Concepts on the Management of the Stroke Patient.** Granada Hills Community Hospital and San Fernando Valley State College Health Sciences Department at Main Auditorium, Speech Building, San Fernando Valley State College, Los Angeles. Saturday-Sunday. Management and Rehabilitation; Role of Anticoagulants; Psychological and Psychiatric Problems; Cerebral-Vascular Accidents in the Young; Headache; Subclavian Steel Syndrome; Extra- and Intra-Cranial Hemodynamic Flow Studies; Echo-Encephalography; Electro-Encephalography; Brain Scanning; Role of Extra-Cranial Vascular Surgery; Angiography. \$10. 16 hrs. Contact: Arno A. Roscher, M.D., Program Chairman, Granada Hills Community Hospital, 10445 Balboa Blvd., Granada Hills 91344. (213) 360-1021.
- May 22-23—**Instrumental Acquisition of Cardiological Data with Clinical Correlation.** American College of Cardiology, Memorial Hospital of Long Beach, and Long Beach Heart Association at Memorial Hospital of Long Beach. Friday-Saturday. Precordial scintillation scanning; special catheters for ventricular function studies; thermomodulation flowmeters; external measurements for ventricular function; new methods of cardiac pacing; use of vectorcardiography for infarct sizing. \$55. 14 hrs. Contact: William D. Nelligan, Exec. Dir., ACC, 9650 Rockville Pike, Bethesda, Md. 20014. (301) 530-1600.
- May 23—**Infectious Problems in Renal Disease.** USC. Saturday. 6 hrs.
- May 25-28—**International Conference on Vascular Diseases of the Brain and Spinal Cord.** American Academy of Neurology, USC and Rancho Los Amigos Hospital at Anaheim Convention Center, Anaheim. Monday-Thursday. U.S. and international papers, rehabilitation team personnel invited. Limited traineeships available. \$125. 18 hrs. Contact: Richard P. Boggs, M.D., Chief, Division of Neurological Sciences, Rancho Los Amigos Hospital, 7601 E. Imperial Highway, Downey 90242. (213) 869-0921.
- June 1-12—**Coronary Care Unit Program for Physicians.** CRMP Area V. See Medicine, May 4-15.
- June 5-6—**Vectorcardiography.** UCSF. Friday-Saturday.
- June 15-July 3—**Coronary Care for Physicians Training Program.** CRMP Area IV. See Medicine, May 4-22.
- June 17-18—**Exercise in Coronary Disease.** USC at Rancho Los Amigos Hospital, Downey. Wednesday-Thursday. 12 hrs.
- June 23-26—**Endocrine Society—Annual Meeting.** Hilton Hotel, San Francisco. Tuesday-Friday. Contact: Nona Lee Mattox, Exec. Sec., ES, 1211 N. Shartel, Oklahoma City 73103. (405) 232-8747.
- Continuously—**Basic Home Course in Electrocardiography.** One year postgraduate series, ECG interpretation by mail. Physicians may register at any time. \$100 (52 issues). Contact: USC.
- Continuously—**Training in the Procedure of Tonometry.** Northern California Society for the Prevention of Blindness at the Glaucoma Screening Clinic, San Francisco. Weekly Saturday morning program in tonometry for internists and general practitioners. Advance appointment required, no charge. 3 hrs. Contact: Frederic S. Weisenheimer, Ed.D., Exec. Dir., NCSBP, 4200 California Street, San Francisco 94118. (415) 387-0934.
- Continuously — **Medico-Surgical Cardiovascular Seminar.** Palo Alto Veterans Administration Hospital, Palo Alto. First Thursday of each month, lectures, demonstrations, seminar discussions, and rounds. Designed

specifically for a selected group of physicians from the Fresno area. Other physicians invited to participate. Contact: William Angell, M.D., Division of Cardiovascular Surgery, Dept. of Surgery, Palo Alto V.A. Hospital, 3801 Miranda Avenue, Palo Alto 94306. (415) 326-5600.

**Continuously—Coronary Care Unit Training for Physicians.** CRMP Area VI and San Bernardino County General Hospital at San Bernardino County General Hospital. Four week courses at monthly intervals, scheduled by arrangement. For practicing physicians working in and directing CCU's. Bedside care, electrocardiography, physical diagnosis, clinical history, therapy, insertion of pacemakers, cardioversion. 160 hrs. Contact: Carl L. Cook, Jr., M.D., San Bernardino County General Hospital, 780 E. Gilbert St., San Bernardino 92404. (714) 885-3411.

**Continuously—Training for Physicians in Nephrology.** CRMP Area VI and LLU at LLU. Courses of four weeks or more available, to be scheduled by arrangement. Bedside conferences, clinical care and management. Hemodialysis, peritoneal dialysis, renal biopsy and kidney transplantation. 160 hrs. Contact: Stewart W. Shankel, M.D., LLU.

**Continuously—Training for Physicians in General Internal Medicine.** CRMP Area VI and LLU at LLU. Four weeks or more, scheduled by arrangement. Bedside and classroom training, practical aspects of clinical care and management. 160 hrs. Contact: LLU.

**Continuously—Training of Physicians in Modern Concepts of Pulmonary Care.** CRMP Area VI, LLU and Riverside General Hospital. Four weeks or more, scheduled by arrangement. Diagnostic and therapeutic methods in medical chest disease, physiological methodology of modern pulmonary care programs, use of new instrumentation in the field. 160 hrs. Contact: George G. Burton, M.D., LLU.

## **Grand Rounds—Medicine**

### **Tuesdays**

8:30-10:00 a.m., Assembly Hall, Harbor General Hospital, Torrance. UCLA.

### **Wednesdays**

10:30-12:00 noon. Auditorium, Medical Sciences Building. UCSF.

11:00 a.m., Room 1645, Los Angeles County-USC Medical Center. USC.

12:30 p.m., Auditorium, School of Nursing, Orange County Medical Center. UCI.

12:30-1:30 p.m., University Hospital, UCSD.

### **Thursdays**

10:30-12:00 noon, Room 33-105, UCLA Medical Center. UCLA.

### **Fridays**

8:00 a.m., Courtroom, Third Floor, Kern County General Hospital, Bakersfield. CRMP Area IV.

8:30 a.m., Auditorium, Lebanon Hall, Cedars of Lebanon Hospital, Los Angeles. CRMP Area IV.

Neurology. 10:15 a.m., held alternately at Stanford University Hospital and Neurology Conference Building 7, V.A. Hospital, Palo Alto. STAN.

1st and 3rd Fridays, 11:00 a.m., Auditorium, Brown

Building, Mount Sinai Hospital, Los Angeles. CRMP Area IV.

1:15 p.m., Lieb Amphitheater, Timken-Sturgis Research Bldg., La Jolla. Scripps Clinic and Research Foundation.

Rheumatology Grand Rounds. 11:45 a.m., Room 6441, Los Angeles County-USC Medical Center, Los Angeles. USC.

## **MENTAL RETARDATION**

May 22-23—**The Mentally Retarded Adult in the Community.** UCSF. Friday-Saturday. \$20. 9 hrs.

June 8-19—**Mental Retardation Workshop.** UCLA and Pacific State Hospital, Pomona, at UCLA Neuropsychiatric Institute. Two weeks. For physicians and allied professionals. Causation, symptomatology, care, treatment and management, diagnostic techniques suitable for office practice, parental reactions and intra-family psychopathology, recent research findings. 80 hrs. Contact: UCLA.

## **OBSTETRICS AND GYNECOLOGY**

May 2-3—**Female Urology.** Tri-County Obstetrical and Gynecological Society at Santa Barbara Billmore Hotel, Santa Barbara. Saturday-Sunday. 10 hrs. Contact: Jack R. Robertson, M.D., 1430 E. Main St., Suite 202, Santa Maria 93454. (805) 925-8759.

May 15-16—**Obstetrics and Gynecology Symposium.** Southern California Permanente Medical Group and Kaiser Foundation Hospitals at Beverly Hilton Hotel, Beverly Hills. Friday-Saturday. Contact: Shirley Gach, Rm. 6014, So. Calif. Permanente Med. Group, 4900 Sunset Blvd., Los Angeles 90027. (213) 663-8411.

## **Grand Rounds—Obstetrics and Gynecology**

### **Mondays**

10-11:30 a.m., Assembly Room, First Floor, Harbor General Hospital, Torrance. UCLA.

### **Fridays**

8 a.m., Auditorium, Orange County Medical Center. UCI.

## **PEDIATRICS**

April 18—**Infectious Diseases.** UCSF at Childrens Hospital, San Francisco. See Medicine, April 18.

April 22-25—**The Hospitalized Child, His Family and His Community.** American Association for Child Care in the Hospital, Stanford Childrens Convalescent Hospital, UCSF and STAN at Sheraton-Palace Hotel, San Francisco. Wednesday-Saturday. 15 hrs. Contact: Helen H. Glaser, M.D., Stanford Childrens Convalescent Hospital, 520 Willow Road, Palo Alto 94304. (415) 327-4800.

May 7-9—**Acute Care in Pediatrics.** UCSF. Thursday-Saturday. Grand Rounds—Management of the Severely Burned Patient; The Dying Child; Cardiopulmonary Emergencies in the Newborn; Hematology and Neurology Emergencies; Endocrine and Renal Emergencies; Infections as an Emergency. \$75. 14 hrs.

May 16-17—**American Academy of Pediatrics—Northern California Chapter.** Four Seasons, Tahoe City. Saturday-Sunday. Light Therapy for Hyperbilirubin-



enemia and Intensive Care in the Nursery; Serious Infections in the Newborn; Genetic Disorders of Metabolism; Cardiac Transplantation; Environmental and Population Problems. \$20. 8 hrs. Contact: Birt Harvey, M.D., 1101 Welch Road, Palo Alto 94304. (415) 325-4482.

May 18-19—**Hearing Problems in Children—Recent Advances.** UCLA. Monday-Tuesday.

May 21-22—**Ear Diseases in Children—Controversial Aspects.** UCLA. Thursday-Friday.

June 5—**Annual Premature Day.** STAN. Friday. \$15.

June 19-21—**Southern California Postgraduate Meeting.** Childrens Hospital of Orange County. Friday-Sunday. Neonatology; Genetics and Inborn Errors of Metabolism; Growth and Endocrinology; Gastroenterology and Shock. \$35. 17 hrs. Contact: Merl J. Carson, M.D., Childrens Hospital of Orange County, 1109 W. La Veta, Orange 92668. (714) 538-8831.

June 24-26—**Annual Pediatric Seminar—The First Ten Months of Life.** Childrens Health Center, San Diego. Wednesday-Friday. \$25. 15 hrs. Contact: David L. Chadwick, M.D., Medical Director, 8001 Frost Street, San Diego 92123. (201) 277-5808.

#### Grand Rounds—Pediatrics

##### Tuesdays

8:00 a.m., Childrens Hospital Medical Center, Oakland.

8:30 a.m., Auditorium, Childrens Division Building, Los Angeles County-USC Medical Center, Los Angeles. USC.

8:30 a.m., Room 4-A, Kern County General Hospital, Bakersfield. CRMP Area IV.

8:30 a.m., Pathology Auditorium, San Francisco General Hospital.

##### Wednesdays

8-9:00 a.m., held alternately at Auditorium, Orange County Medical Center and Auditorium, Childrens Hospital of Orange County. UCI.

8:30 a.m., Bothin Auditorium, Childrens Hospital, San Francisco.

##### Thursdays

8:30-10:00 a.m., Room 664, Science Building, UCSF.

8:30-9:30 a.m., Lebanon Hall, Cedars of Lebanon Hospital, Los Angeles.

8:30 a.m., First Floor Auditorium, Harbor General Hospital, Torrance.

##### Fridays

8:00 a.m., Lecture Room, A Floor, Health Sciences Center, UCLA. CRMP Area IV.

8:30 a.m., Stanford University Medical Center, Palo Alto.

8-9:00 a.m., Lecture Hall, Childrens Hospital of Los Angeles.

Infectious Disease Grand Rounds. 10:00 a.m., Auditorium, Childrens Division Building, Los Angeles County-USC Medical Center, Los Angeles. USC.

#### PSYCHIATRY

April 18 & 25—**Critical Issues in Mental Health.** University of California Extension, Riverside, at Cafeteria, University Commons, UC Riverside. Two Saturdays. 14 hrs. Contact: Ray Olitt, Health Services Coordinator, UC Extension, Riverside 92502. (714) 787-4329.

May 2—**Use of Imagination in Psychotherapy.** UCSF. Saturday. Dreams and Fantasies in Psychoanalytically Oriented Psychotherapy, Images in Jungian Therapy, Image Formation Techniques in Gestalt Therapy, Systematic Desensitization—A Form of Behavior Therapy, Implosive Therapy, Uses of Image Formation in Other Schools of Therapy. \$15. 5½ hrs.

May 2-3—**Explorations and Process in Group Therapy.** UCSF at Modesto Junior College, Modesto. Saturday-Sunday.

May 7-11 — **American Psychoanalytic Association.** Sheraton Palace Hotel, San Francisco. Thursday-Monday. \$15 for non-members. 21 hrs. Contact: Mrs. Helen Fischer, Exec. Sec., APA, 1 East 57th Street, New York 10022. (212) 265-0430.

May 8-10—**American Academy of Psychoanalysis—Annual Meeting.** Jack Tar Hotel, San Francisco. Friday-Sunday. Psychoanalysis and the Newer Therapies. \$5 non-members. 15 hrs. Contact: Mollie Carroll, 125 East 65th Street, New York 10021. (212) 879-8950.

May 8-10—**Society for Biological Psychiatry.** Hilton Hotel, San Francisco. Friday-Sunday. Personality Disorders. 24 hrs. Contact: George N. Thompson, M.D., Sec.-Treas., SBP, 2010 Wilshire Blvd., Los Angeles 90017. (213) 483-7863.

May 9—**American College of Psychiatrists — Annual Meeting.** Fairmont Hotel, San Francisco. Saturday. Contact: Melvin Sabshin, M.D., University of Illinois, Medical Center, P.O. Box 6998, Chicago 60680. (312) 663-7000.

May 9-10—**Psychiatry and the Law.** UCSF at Benbow Inn, Garberville. Saturday-Sunday. Legal Aspects of Mental Illness in California; Suicide, Faith and Society; Deviant Behavior; The Draft Law and the College Counselor; The Lanterman-Petris-Short Act; The Concept of Diminished Capacity in Forensic Psychiatry; Guilt; Psychiatrist as Expert Witness; Drugs, Youth and Legal Restraints. \$25. 8½ hrs.

May 10—**Association for the Advancement of Psychotherapy.** Civic Auditorium, San Francisco. Sunday. The Role of Psychotherapy in the Treatment of Depressed Suicidal Patients. \$5. Contact: Stanley Lesse, M.D., Pres., AAP, 15 W. 81st Street, New York 10024. (212) 873-9233.

May 10—**American Society for Adolescent Psychiatry —Annual Clinical Conference.** Hilton Hotel, San Francisco. Sunday. Identity—Clinical Aspects; The Spectrum of Adolescent Therapies; "High School"; Etiology of Three Current Adolescent Syndromes—An Hypothesis. 5 hrs. Contact: Herman D. Staples, M.D., Sec., ASAP, 24 Green Valley Rd., Wallingford, Pa. 19086. (215) 556-1054.



May 11-15—**American Psychiatric Association.** Civic Auditorium and Brooks Hall, San Francisco. Monday-Friday. Contact: Robert S. Garber, M.D., Exec. Sec., Carrier Clinic, Belle Mead, New Jersey 08502. (201) 359-3101.

May 14-16—**Mental Health — 2½ Day Symposium.** UCSF. Thursday-Saturday.

May 16-17—**Progress in Psychotherapy.** UCSF at Napa State Hospital, Imola. Saturday-Sunday.

May 23-24—**Residential Care for the Mentally Ill Patient.** UCSF at DeWitt Hospital, Auburn. Saturday-Sunday.

June 26-28—**Comparative Psychotherapies.** USC Division of Postgraduate Psychiatry at Sahara Tahoe Hotel, Lake Tahoe. Friday-Sunday. \$50. Contact: Donald F. Naftulin, M.D., Director, Division of Postgraduate Psychiatry, USC. (213) 225-1511, ext. 336.

## **RADIOLOGY—PATHOLOGY**

April 17-30—**Radiology of the Gastrointestinal Tract.** USC, Princess Carla Cruise to Mexico from Los Angeles. Two weeks. \$200. 28 hrs.

May 9—**Diseases of the Gastrointestinal Tract.** South Bay Radiology Society and South Bay Pathology Society at Carmel Theater, Carmel. Saturday 1:30-5:30. Separate morning workshop in tube biopsy processing technique and interpretation. 4 hrs. Contact: Robert Rinehart, M.D., Dept. of Pathology, Santa Clara Valley Medical Center, 751 South Bascom Ave., San Jose 95128. (408) 293-0262, ext. 491.

May 16—**Radiology Society of Southern California.** Hotel del Coronado, Coronado. Saturday. Contact: Gladden V. Elliott, M.D., 5565 Grossmont Center Drive, Suite 1, La Mesa 92041.

Continuously—**Principles and Clinical Uses of Radioisotopes.** UCSF. Fundamentals for the proper understanding and use of radioactivity in clinical medicine. Training in diagnostic and therapeutic uses of radioisotopes. Normal period of training: 3 months. Two part course: Part A, Basic Fundamentals; Part B, Clinical Applications.

Continuously — **Mammography.** UCSF Mammography Section, Department of Radiology. Three days weekly, beginning with Tuesday. Call several days in advance. Contact: Richard H. Gold, M.D., Mammography Section, Department of Radiology, UCSF. (415) 666-1918.

## **Grand Rounds—Radiology**

### **Fridays**

Neuroradiology Grand Rounds. 9:30 a.m., held alternately at Stanford University Hospital and Neurology Conference Building 7, V.A. Hospital, Palo Alto, STAN.

## **SURGERY—ANESTHESIOLOGY**

May 2—**Recent Developments in Anesthesiology.** Palo Alto Medical Clinic and Research Foundation, Palo Alto. Saturday. Ketamine, Saunders Ventilator, Arrhythmias, Preparation of Respiratory Patient for

Surgery. \$10. 6 hrs. Contact: John Damron, M.D., Palo Alto Medical Clinic, 300 Homer Ave., Palo Alto 94301. (415) 321-4121.

June 4-6—**Highlights of Ophthalmology.** PMC Department of Ophthalmology at PMC. Thursday-Saturday. Cryosurgery, Fluorescein angiography, glaucoma, cataract surgery, diabetic retinopathy, retinal detachment, adhesives in surgery, contact lenses and ultrasonography. \$125. Contact: Wayne L. Erdbrink, M.D., Director of Residency Training, Dept. of Ophthalmology, PMC.

June 4-6—**Rheumatoid Arthritic Surgery.** UCSF and American Academy of Orthopaedic Surgeons at UCSF. Thursday-Saturday. \$150. 17½ hrs. Contact: UCSF.

June 12-13—**Le Roy C. Abbott Orthopedic Society—Annual Meeting.** University of California Hospital, San Francisco. Friday-Saturday. 8 hrs. Contact: William S. Cappeller, M.D., Sec.-Treas., LCAOS, 450 Sutter Street, San Francisco 94108. (415) 397-4455.

June 12-14—**California Society of Anesthesiologists—4th Biennial Scientific Meeting.** Sahara-Tahoe Hotel, South Shore, Lake Tahoe. Friday-Sunday. The Anesthesiologist and His Relationship to Other Specialties. 8 hrs. Contact: Norman R. Catron, Exec. Sec., CSA, 100 So. Ellsworth Ave., Suite 401, San Mateo 94401. (415) 343-4644.

## **Grand Rounds—Surgery**

### **Wednesdays**

7:15 a.m., Auditorium, Kern County General Hospital, Bakersfield. CRMP Area IV.

1st and 3rd Wednesdays. 11:00 a.m., Auditorium, Brown Building, Mount Sinai Hospital, Los Angeles. CRMP Area IV.

### **Thursdays**

Neurology and Neurosurgery Grand Rounds. 11:00-12:15. Room 663, Science Building, UCSF.

### **Fridays**

1-2:00 p.m., Auditorium, Orange County Medical Center, Orange. UCI.

Neurosurgery. 11:15 a.m., held alternately at Stanford University Hospital and Neurology Conference Building 7, V.A. Hospital, Palo Alto, STAN.

### **Saturdays**

8:00 a.m., Auditorium, 1st floor, University Hospital of San Diego County, San Diego. UCSD.

9:00 a.m., Room 73-105, Health Sciences Center, UCLA. CRMP Area IV.

8:30 a.m., Assembly Room, Harbor General Hospital, Torrance. CRMP Area IV.

## **OF INTEREST TO ALL PHYSICIANS**

April 17-18—**Infectious Diseases.** UCSF. See Medicine, April 17-18.

April 19—**Office Emergencies: A Symposium for Medical Assistants.** UCSF. Sunday. \$12.50. 6 hrs.

April 23-25—**First Annual Hospital Medical Staff Conference—Medical Staff Leadership: Fact or Fic-**

tion. USC and CRMP Area V at Monte Corona Conference Center, Twin Peaks. Thursday-Saturday. \$100. 18 hrs.

April 25-26—**Sex in Modern Society.** UCSF at Flamingo Hotel, Santa Rosa. Saturday-Sunday. \$15. 8 hrs.

May 1-2—**Trauma—Immediate Care.** UCSF at Mary's Help Hospital, Daly City. Friday-Saturday. Initial Evaluation of Injured Patient; Cranio-Cerebral Injuries and the Unconscious Patient; Thoracic Injuries; Abdominal Trauma; Hemorrhagic Shock and Intravascular Coagulation; Vascular Injuries; Radiology; Acute Orthopedic Problems; Treatment of the Broken Hip and Wrist; The Knee; Orthopedic and Neurological Aspects of Broken Neck and Back; Fractures in Children. \$40.

May 3-9—**Hawaii Medical Association.** Hawaiian Village, Honolulu. Sunday-Saturday. Contact: Miss Lee McCaslin, Exec. Sec., HMA, 510 Beretania Street, Honolulu 96813. (808) 536-7702.

May 6—**Annual Seminar—N.E. Sub-Chapter, Los Angeles County Academy of General Practice.** Santa Teresita Hospital, Duarte. Wednesday. Alcoholism and Dangerous Drugs. \$15. 3 hrs. Contact: John A. Corbin, M.D., 924 Buena Vista Avenue, Duarte 91010. (213) 358-455.

May 8-9—**Population Explosion, Birth Control, Sexual Revolution.** University of California Extension, Riverside, at Watkins Hall, UC Riverside. Friday-Saturday. 10 hrs. Contact: Ray Olitt, Health Services Program Coordinator, UC Extension, Riverside 92502. (714) 787-4329.

May 16-17—**Economic Organization of the Physician.** UCSF at Hilton Hotel, San Francisco. Saturday-Sunday. \$75. 12½ hrs.

May 20—**Medical Practices in Central America and Mexico.** Agnews State Hospital at Agnews State Hospital, San Jose. Wednesday. 1½ hrs. Contact: J. Elizabeth Jeffress, M.D., Agnews State Hospital, San Jose 95114. (408) 262-2100.

May 22-23—**Teenage Pregnancies.** USC at International Hotel, Los Angeles. Friday-Saturday. Medicine, Education, Law, Social Services. 12 hrs.

May 22-24—**California Medical Assistants Association—Annual Convention.** International and Hilton Hotels, Los Angeles. Friday-Sunday. Contact: Kay Marsh, 7271 Katella Avenue #19, Stanton 90680. (714) 828-3525.

May 29-July 1—**Medical Centers of Europe.** USC. Five weeks. Visiting medical centers in Dublin, London, Amsterdam, Moscow, Vienna, Rome, Venice-Lido, Paris.

June 17—**Income Maintenance Predicated on Reproductive Responsibility: A New Approach To The Prevention of Mental Illness Due to Ignorance, Poverty, and Overcrowding.** Agnews State Hospital, San Jose. Wednesday. 1½ hrs. Contact: J. Elizabeth Jeffress, M.D., Agnews State Hospital, San Jose 95114. (408) 262-2100.

June 18-July 9—**Medical Centers of Africa 1970.** USC in Africa. Three weeks. Visiting Senegal, Ivory Coast, Ghana, Uganda, Kenya, Tanzania. \$1699.

June 21-25 — **American Medical Association.** Palmer House, Chicago. Sunday-Thursday. Contact: Ernest B. Howard, M.D., Exec. Vice-Pres., AMA, 535 N. Dearborn St., Chicago 60610. (312) 527-1500.

Continuously—**Audio-Digest Foundation.** A non-profit subsidiary of CMA. Twice-a-month tape recorded summaries of leading national meetings and surveys of current literature. Services by subscription in: General Practice, Surgery, Internal Medicine, Ob/Gyn, Pediatrics, Anesthesiology, Ophthalmology. Catalog of lectures and panel discussions in all areas of medical practice also available. Contact: Mr. Claron L. Oakley, Editor, 619 S. Westlake Ave., Los Angeles 90057.

## TELEVISION

**Southern California's Medical Television Network.** UCLA. Weekly broadcasts, Tuesdays 8:30 a.m. Contact: UCLA Medical Television. (213) 825-2071.

April 21—**Malnutrition.** Medical Television Network.

April 28—**Management of Schizophrenia in the Community.** Medical Television Network.

May 5—**Initial Workup of Hypertension.** Medical Television Network.

May 12—**Preventive Medicine.** University of Western Ontario.

May 19—**Psoriasis.** British Broadcasting Corporation.

May 26—**Breakthroughs in Malignant Diseases.** Medical Television Network.

**Santa Clara County Medical Society's MD-TV.** Weekly broadcasts. Thursdays 8:30 p.m. Channel 54, Greater San Jose Area. Of educational value to both physicians and nurses. Contact: Roger Brown, Santa Clara County Medical Society, 700 Empey Way, San Jose 95128. (408) 286-5050.

## CMA Postgraduate Institutes and Circuit Courses

May 8-9—**San Joaquin Valley Counties Regional Postgraduate Institute.** CMA, USC, and Fresno County Medical Society at Ahwahnee Hotel, Yosemite. Friday-Saturday. Concurrent symposia in Adolescent Medicine, Sensitivity Training, Hematology, Coronary Care, The Medical School and the Practicing Community. \$20. 10 hrs. Contact: CMA

May 15-16 — **Redwood Regional Conference.** CMA, UCSF at Konocti Harbor Inn, Clear Lake. Friday-Saturday. The Anemic Patient and Musculo/Skeletal Disorders. \$20. Contact: CMA.

June 18-20—**Sacramento Valley Counties Regional Postgraduate Institute.** CMA, UCLA and Sacramento County Medical Society at Cal Neva Lodge, North Lake Tahoe. Thursday-Saturday. Cerebral Vascular Disease including Rehabilitation and the Surgical and Medical Management of Cardiac Disease, Delivery of Health Care in the '70s. \$20. 12 hrs. Contact: CMA.



# BOOK REVIEWS

CALIFORNIA MEDICINE does not review all books sent to it by the publishers. A list of new books received is carried in the Advertising Section.

**PHARMACOLOGICAL, CONVULSIVE AND OTHER SOMATIC TREATMENTS IN PSYCHIATRY** — Lothar B. Kalinowsky, M.D., Clinical Professor of Psychiatry, New York Medical College, New York, New York; Hanns Hippus, M.D., Professor of Psychiatry, Free University, Berlin, Germany; Grune & Stratton, Inc., 381 Park Avenue South, New York, N.Y. (10016), 1969. 470 pages, \$14.75.

For almost 25 years the collaborative volume by Lothar Kalinowsky and Paul Hoch was the standard work on somatic treatments in psychiatry for American psychiatrists and for many English-speaking physicians around the world. Between 1946 and 1961 Kalinowsky and Hoch took their book through three editions, a reflection of the dramatic expansion of the field through those decades which saw the consolidation of the place of electroconvulsive therapy, the first use of the phenothiazines in psychiatry, the beginning of antidepressant drug treatment, and major revisions in the roles of insulin therapy and psychosurgery.

Paul Hoch died in 1965. In the current (fourth) version of the monograph Kalinowsky's coauthor is Hanns Hippus, M.D., Professor of Psychiatry at Berlin's Free University. Dr. Hippus' special interest in psychopharmacology may be responsible for what seems to distinguish this edition most from its predecessors, e.g. a much-enlarged section on pharmacotherapy (152 vs. 117 pages) which includes detailed consideration, for example, of 23 antipsychotic drugs, of which ten are seldom or never used in this country.

Overall, however, the organization and emphases of the new edition follow closely those of the last version. The chapter on insulin coma and subcoma has been shortened, and the superb final chapter entitled "Theoretical Remarks" has been updated and revised. There are excellent discussions of the anti-anxiety agents (which the authors unfortunately continue to call "tranquilizers"), antidepressants and stimulants. The enlarged section on "The Convulsive Therapies" remains a model of scholarship and sound clinical judgment.

Aside from its mildly pedantic and encyclopedic style, the book's faults are minor. We would argue, for example, with its assertion that combinations of psychoactive drugs with ECT are without advantage and should be avoided altogether: We and others have used such combinations in selected cases for over a decade to good effect and without mishap. Also, while they recognize that intravenous barbiturate anaesthesia during ECT is a major hazard to the patient, Kalinowsky and Hippus do not consider alternatives to routine barbiturate anaesthesia as extensively as they might. Anaesthesia can be avoided in all but a few instances with sufficient attention to the patient's psychological environment and to staff attitudes; without anaesthesia the need for an anaesthesiologist and patient morbidity both decline. Finally, while the sound clinical balance of the chapter on psychosurgery is a tribute to the

authors, one might question the value of so large an amount of space devoted to these procedures, and especially the detailed neuroanatomical discussions of a great many operative approaches and their variations.

For those of us whose copies of the last edition of Kalinowsky and Hoch were thumbworn as well as increasingly out of date, this revision by Kalinowsky and Hippus is welcome indeed. In the final paragraph of their Preface, the authors write:

"Psychiatry is still—exactly as at the time of the first writing of this book in 1946—limited to purely empirical treatments of diseases whose origin remains shrouded in mystery. This state of affairs makes it all the more gratifying that active application of so many different therapeutic methods can restore the functioning of an increasing number of psychiatric patients. The awareness of constant progress, and the realization of the need for better integration of available treatments, encouraged us to rewrite this book."

They have been successful in an increasingly difficult undertaking, and the result is certainly a credit to them. It would be hard to imagine any physician with an interest in any aspect of somatic treatment in psychiatry who won't have this volume on his bookshelf.

MORTON R. WEINSTEIN, M.D.

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**THE CIBA COLLECTION OF MEDICAL ILLUSTRATIONS**—Volume 5—Heart—(A Compilation of Paintings on the Normal and Pathologic Anatomy and Physiology, Embryology, and Diseases) —Prepared by Frank H. Netter, M.D.; Edited by Fredrick F. Yonkman, M.D., Ph.D. Commissioned and published by CIBA. CIBA Pharmaceutical Company, Division of CIBA Corporation, 556 Morris Avenue, Summit, N.J. (07901), 1969. Copies may be ordered from the Publications Section, CIBA Pharmaceutical Company, 556 Morris Avenue, Summit, N.J. (07901). 295 pages, \$29.50 (sold at cost).

This atlas is an ambitious undertaking—the fifth volume of medical illustrative volumes featuring the drawings by Dr. Frank H. Netter. It covers five sections: anatomy, physiology, embryology, congenital diseases and acquired diseases of the heart. It presents drawings of the heart, supplemented by semi-diagrammatic sketches, microscopic sections as well as reproductions of roentgenograms, angiograms, pressure curves, electrocardiograms, phonocardiograms and other necessary visual material for correlation of function to structure. The illustrator and the editor of the atlas are aided by a distinguished list of 49 contributors and consultants. The wealth of the material, which contains such ancillary features as technique of resuscitation, various surgical techniques, including that of cardiac transplantation, makes it a complete atlas dealing with the heart. Its teaching value at all levels—from the medical student to the sophisticated expert in the field of cardiology—is unquestioned and it can be highly recommended as a valuable addition to the



library of any hospital and every physician dealing with cardiovascular diseases. It has certain negative features, which are common to the basic concept of an atlas; namely, graphic presentation of the many controversial subjects allows only a dogmatic exposure, emphasizing a particular view. One could take many issues with the presentation of data dealing with clinical physiology and phonocardiography. I am sure, some surgeons might take issue with the presentation of surgical details! Nevertheless, when the reader recognizes that some presentations cannot be taken literally, and uses it accordingly, he will find a beautifully published, richly illustrative exposure of the field of cardiology which is well worth consulting and browsing through to find graphic presentation of his daily clinical problems.

ARTHUR SELZER, M.D.

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**MICRONEUROSURGERY**—Robert W. Rand, Ph.D., M.D., Professor of Neurological Surgery, University of California School of Medicine, Los Angeles. The C. V. Mosby Company, 3207 Washington Boulevard, St. Louis, Mo. (63103), 1969. 224 pages, with 16 contributors, 257 illustrations, including one color plate, \$25.00.

Introduction of the surgical microscope gave an exciting new perspective to neurosurgical techniques. Robert Rand was one of the first American neurosurgeons to recognize the role of microsurgery in the central nervous system, and no one is better prepared to produce a major monograph on this subject.

In one sense, *Microneurosurgery* is a manual of microsurgery. Its introductory chapters contain detailed descriptions of the microscope, microsurgical instruments, and microsurgical anatomy. Its remaining chapters discuss the use of the surgical microscope in problems that are specifically neurosurgical.

Most of the 17 chapters were written by Rand. In one chapter, he presents the transfrontal-transsphenoidal approach to pituitary tumors, which has a distinct advantage in selected cases and in all cases reduces the degree of frontal-lobe retraction required for adequate exposure of intrasellar lesions. In another chapter, he describes the occipital trans-meatal technique for total extirpation of acoustic tumors with preservation of the facial nerve. Convincingly, he argues for this approach to acoustic tumors of all sizes. Chapters on the microsurgical treatment of cerebral aneurysms, and of spinal-cord tumors and vascular malformations are all accounts of Rand's personal experience.

Additional chapters were contributed by men who have developed particular microsurgical techniques: James Smith on peripheral nerves, Jules Hardy on transsphenoidal hypophysectomy, and Peter Jannetta on transtentorial trigeminal rhizotomy. Microvascular techniques are described by Khodadad, Buncke and Murray, and by Krayenbuhl and Yasargil.

This book is well written and beautifully illustrated, and I recommend it to anyone curious about the emergence of microneurosurgery.

CHARLES B. WILSON, M.D.

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**THE ACUTE ABDOMEN** — By Thomas W. Botsford, M.D., F.A.C.S., Surgeon, Peter Bent Brigham Hospital; Associate Clinical Professor of Surgery, Harvard Medical School; and Richard E. Wilson, M.D., F.A.C.S., Senior Associate in Surgery, Peter Bent Brigham Hospital; Associate Professor of Surgery, Harvard Medical School. Volume X in the Series MAJOR PROBLEMS IN CLINICAL SURGERY, J. Englebert Dunphy, M.D., Consulting Editor. W. B. Saunders Company, West Washington Square, Philadelphia, Pa. (19105), 1969. 179 pages, \$8.00.

Every medical student and physician is familiar with Cope's Book on the Acute Abdomen. This book, written by an Englishman, has been a classic in its field and until

the appearance of this work by Botsford and Wilson on *The Acute Abdomen*, nothing to rival it has appeared in the American literature. *The Acute Abdomen* is a constant challenge to every physician with respect to diagnosis and appropriate therapy. Many new adjuncts have appeared which are helpful to the clinician in the diagnosis of the acute abdomen and it is timely that a current monograph appear on this subject from American sources.

The fundamental clinical processes producing the acute abdomen have not changed in the past 25 years, but our understanding of the diagnosis and treatment has, e.g., the detection and management of the acute ruptured abdominal aneurysm was a rarity prior to 1950, but must nowadays be uppermost in the mind of every clinician observing an acute abdominal complaint in the elderly patient for its early recognition and treatment may be lifesaving. The new adjuncts to abdominal diagnosis ranging from emergency radiological investigation to the use of isotopes with appropriate organ scanning to the detection of unusual disorders by angiography of the vascular system of the abdomen are all discussed and illustrated in this excellent monograph. From these emerge new approaches to therapy in the acute abdomen and the relevance of the newer diagnostic techniques is amply discussed in the light of therapeutic measures currently available.

Supportive care both pre and postoperatively has also advanced considerably in recent years. The appropriate antibiotic, the desirable fluid to be infused, the physiologic support which may be lifesaving, are all reviewed in the management of the acute abdomen both preoperatively and postoperatively in this volume.

The book itself is divided into six sections: section 1 discusses the clinical tools available for diagnosis and treatment, section 2 reviews abdominal trauma, section 3 covers acute abdominal inflammatory diseases, section 4 discusses intestinal obstruction, section 5 reviews hemorrhages as cause of the acute abdomen, and section 6 emphasizes postoperative management of the acute abdominal problems. The book is short, simply and clearly written, beautifully illustrated with x-rays, diagrams, and clear line drawings and in every way is a highly commendable monograph.

I have no hesitation at all in recommending this monograph to medical students, interns, residents and practicing physicians. It is a valuable, modern contribution to our understanding of the acute abdomen.

VICTOR RICHARDS, M.D.

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**THE PRINCIPLES AND PRACTICE OF MEDICINE**—17th Ed.—Edited by A. McGehee Harvey, M.D., D.Sc. (Hon.), Professor of Medicine and Director of the Department of Medicine, The Johns Hopkins University School of Medicine, Physician-in-Chief, The Johns Hopkins Hospital; Leighton E. Cluff, M.D., formerly Professor of Medicine, The Johns Hopkins University School of Medicine; presently Professor and Chairman, Department of Medicine, University of Florida College of Medicine, Gainesville; Richard J. Johns, M.D., Professor of Medicine, The Johns Hopkins University School of Medicine; Director of the Sub-department of Biomedical Engineering; Albert H. Owens, Jr., M.D., Associate Professor of Medicine, The Johns Hopkins University School of Medicine; David Rabinowitz, M.D., Assistant Professor of Medicine, The Johns Hopkins University School of Medicine; and Richard S. Ross, M.D., Professor of Medicine and Associate Professor of Radiology, The Johns Hopkins University School of Medicine. Appleton-Century Crofts (Division of Meredith Publishing Company), 440 Park Ave. South, New York, N.Y. (10016), 1968. 1472 pages, \$22.50.

A reviewer of the first edition of 1892 of William Osler's famous textbook of medicine commented upon the originality of the work in that it contained no Preface. But for the Preface and the notice of previous copyrights it would be hard to associate the present textbook as having any relationship whatsoever with its distinguished progenitor of which it purports to be the seventeenth edition (Osler's

title was not original) since it is so totally different in aims and in spirit.

In their Preface the new editors draw attention to a letter from Osler at the time of the 7th edition in which he expressed the hope that it might be arranged "to have the work kept up as a Johns Hopkins Textbook of Medicine." Although this did not come to pass with succeeding editors, the present editorial board in resuscitating the text decided not only to follow Osler's wish but to give it an entirely new direction so as to serve in complementary fashion to existing encyclopaedic texts by emphasizing clinical problems rather than disease entities and, as they put it, "to describe and define the way in which the experienced physician approaches the solution and management of such problems."

However, in the Foreword the aims expressed in the Preface seem to have been lost sight of and new directions are adumbrated. Now we are told periphrastically that medical practice deals with three basic questions—diagnosis, therapy and prognosis—to which is added, in a manner reminiscent of sophistical medievalism, a fourth question "Why did it happen?" (presumptively substituted for the "how") since this "imposes a responsibility to contribute to a better understanding of causation and prevention." The editors go on to say, with doubtful logic, that the usual textbooks do not prepare the practitioner to answer these questions since they are disease rather than patient oriented. They conclude by saying that "it is our purpose to produce a book which is built around the patient rather than the disease" but it is to include diagnosis, management, prognosis, "methods employed in acquiring factual data, the discriminating use of ancillary diagnostic techniques, and the systematic analysis of the accumulated information" as well as providing basic information on the various manifestations of disease and their natural history.

To accomplish these aims the work is divided into 19 sections with numerous (150) subsections. The scope of the text perhaps can be best appreciated by a simple listing of these main titles: 1. The Approach to the Patient, 2. Disorders of Water and Electrolyte Metabolism, 3. Renal Diseases and Disturbances in Renal Function, 4. Cardiovascular Disease, 5. Pulmonary Disease, 6. Medical Genetics, 7. Hematology, 8. Neoplastic Diseases, 9. Infectious Diseases, 10. Diseases with Immunologic Features, 11. Diseases of Joints, 12. Diseases of the Gastrointestinal Tract, 13. Diseases of the Liver, Including Jaundice, 14. Endocrinology, 15. Disorders of the Nervous System, 16. Psychiatry in Medicine, 17. Diseases of Medical Management, 18. Medical Emergencies, 19. Ocular and Cutaneous Manifestations of Disease. The unusual features of the approach and arrangement are immediately apparent from the main titles.

As the old adage has it, the proof of the pudding is in the eating thereof, so the value of a textbook depends upon its acceptance. Despite Harvey Cushing's statement to the contrary, the original Osler was received with indifference by the majority of the journals of the day and received favorable notice in the JAMA only with the second edition of 1895. Whether the present text is moving in important new directions only time can tell.

Since no reviewer can pretend to the breadth of expertise necessary for a critical examination of the text in detail he can only give general impressions. The text, despite the rather specious claims of the Preface and Foreword, is in reality a series of clinical lectures similar in style and purpose to those common in medical schools of 40 years ago. In each section there is the presumption that the student needs a review of his anatomy, physiology, bio-

chemistry and other basic science material. This may be a useful pedagogic device but consumes an inordinate amount of space at the expense of other subsections and one wonders how students got to their clinical years without being completely familiar with such elementary material. Symptomatology, physical, laboratory and differential diagnosis of the various systems is discussed, followed by the principles of therapy and prognosis in the various clinical complexes and categories. Much of the information is presented in tabular form or illustrated by means of line diagrams. In summary, the text attempts to integrate a vast amount of material for the student, much of which he should be doing for himself. Consequently much of the writing is unduly condensed and, unlike its forbears, is more a single volume of reference, not very easy to read, but this may have appeal for some and be only utilitarian to others. Despite the aims of the editors, the patient seems once more to have disappeared in the welter of tabulations and medical technology.

JOHN B. DEC. M. SAUNDERS, M.D.

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RENAL DISEASE IN CHILDHOOD—John A. James, M.B. (Edin.), M.R.C.P., D.C.H., Professor of Pediatrics, Department of Pediatrics, University of Southern California School of Medicine, Los Angeles, Head Physician, Pediatric Inpatient Services, Los Angeles County-University of Southern California Medical Center, Los Angeles. The C. V. Mosby Company, 3207 Washington Boulevard, St. Louis, Mo. (63103), 1968. 371 pages, \$18.50.

Recent therapeutic advances in successful homotransplantation, dialysis technique, and effective drug therapy justify the publication of this book oriented toward the practicing physician. The author collaborated in early electromicroscopy studies but subsequently became more interested in the clinical aspects of renal disease. His text is carefully written, wastes few words, and concerns mainly the major renal problems encountered in childhood. The author emphasizes diagnosis and treatment rather than controversial details of etiology, pathology or pathogenesis. The book therefore serves as a practical guide for the medical treatment of renal disease rather than as a textbook. The writing is flavored with much personal observation and experience gained in the pediatric renal clinics of Los Angeles County General Hospital. The style is concise and informal and will appeal to the tired practitioner who must keep up with his reading late at night or between calls on weekends.

Most physicians ten years past graduation will welcome the uncomplicated introductory review of normal anatomy, embryology, physiology and current diagnostic procedures. Many helpful diagrams and unusually clear x-ray reproductions supplement this section of the text. Recent developments in studies of neonatal kidney function are described with a caution against the pitfalls in planning therapeutic regimens for the newborn. Congenital anomalies are classified and described succinctly but adequately. Little detail of surgical technique is described but this is probably unnecessary in a medically-oriented book.

Chapters on glomerulonephritis and nephrosis will be of considerable interest to the practicing physician since the author frequently includes practical advice derived from his own clinical experience. This includes his own simplified classification of nephritis in addition to a review of previous classifications. The section on urinary tract infection also reflects the author's personal and authoritative experience. This chapter merits reading in detail by the pediatrician since it emphasizes the importance of careful, accurate management and follow-up of this common problem. Chapters on acute and chronic renal failure include the indications for and the technique of dialysis and also a useful table on modified antibiotic dosage.



Under miscellaneous disorders, several recently reported diseases such as hemolytic-anemia syndrome, Alport's syndrome, and primary renal tubular disorders are described clearly and adequately. However, only five short paragraphs are devoted to discussion of the relatively more common renal tumors, e.g., Wilm's. Neuroblastoma is covered in one sentence. Again, these are primarily surgical problems. A final chapter brings the reader up to date on problems of dialysis and kidney transplantation.

When a test is limited to basic information, a few omissions may occur. The author does not evaluate the results of treatment of chronic nephritis with cytotoxic drugs. The incidence of hypertension in uncomplicated nephrosis is not indicated. In spite of an illustration of acute glomerulonephritis following impetigo, the author recommends only local therapy for the skin. The state dosage of erythromycin for treatment of streptococci is lower than the manufacturer's recommendation. The theoretical academician will object to the lack of detailed discussion. However, the hurried practitioner will appreciate the frequent "cook-book" style of recommendations for treatment and can consult the adequate bibliography for more information if desired.

Because the style is so clear and direct, the 350 pages of the text can be read in four evenings by any busy physician. Residents in pediatrics and urology will find the concise directions invaluable in writing hospital orders.

Pediatricians, generalists and urologists who serve children should keep this book at a ready place on their library shelf and will find themselves referring to it almost daily.

WILLIS A. WINGERT, M.D.

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**SURGERY OF THE CHEST**—Second Edition—With the Collaboration of 48 Authorities—Edited by John H. Gibbon, Jr., M.D., formerly Samuel D. Gross Professor of Surgery and Chairman of the Department of Surgery, The Jefferson Medical College, Philadelphia; David C. Sabiston, Jr., M.D., Professor and Chairman, Department of Surgery, Duke University School of Medicine, Durham, North Carolina; and Frank C. Spencer, M.D., George David Stewart Professor of Surgery and Chairman of the Department of Surgery, New York University School of Medicine, New York, New York. W. B. Saunders Company, West Washington Square, Philadelphia, Pa. (19105). 954 pages, \$52.50.

Since the publication of the first edition of this book, edited by John H. Gibbon, Jr., M.D., in 1962, the expansion of knowledge in the field of thoracic surgery has been extremely rapid. The second edition, in which Dr. Gibbon is assisted by David C. Sabiston, Jr., M.D., and Frank C. Spencer, M.D., faithfully records the changes which have occurred in this field in the past decade. The number of chapters has been increased from 32 to 42 and the number of authors from 36 to 51, but the number of pages has changed only slightly (from 902 to 954). As a result, this textbook is successful in being complete but fails to be comprehensive. The limited number of pages allowed to each subject results in many chapters being merely descriptive rather than critical.

The first 11 chapters cover the general management of thoracic surgical patients. The introductory chapter on Cardiorespiratory Dynamics by Myron B. Laver and W. G. Austen reflects new knowledge of the pathophysiologic effects of cardiopulmonary surgery, but it assumes considerable basic knowledge on the part of the reader. Many readers may prefer the original discussion of this subject by Gibbon in the first edition. An excellent chapter by William E. Adams on Preoperative Evaluation of Pul-

monary Function is retained. The chapter on Postoperative Management by Gibbon and Richard T. Padula does not adequately reflect improvements in this area made in the last few years. The treatment of postoperative low cardiac output is not included. The most noteworthy addition to this section of the book is the chapter by Spencer and John F. Daly on Tracheostomy and Assisted Ventilation.

The section of the book which covers pleuropulmonary surgery has undergone very little change. The coverage given to carcinoma of the lung, perhaps the most common problem handled by thoracic surgeons, continues to be noticeably short. The solitary pulmonary nodule is covered in one-half page. Although a very good chapter by Herbert C. Maier on the pleura contains a description of the technique of thoracentesis, the technique of closed thoracotomy is not covered anywhere in the book.

The section on cardiovascular diseases has been entirely revised. By and large the chapters are short and tend to be descriptive, but several are quite good and contain extensive bibliographies. Excellent critical treatment of their subjects is achieved by William M. Chardack on pacemakers, John W. Kirklin on ventricular septal defect, Clarence Dennis on assisted circulation, Sabiston on pulmonary embolism and transplantation of the heart by Eugene Dong and Norman Shumway. Notably deficient is the chapter by Donald B. Effler and William C. Sheldon on myocardial revascularization, which reflects only the opinions of the authors and contains only seven references to work other than their own in this extremely active and important area.

This textbook will continue to serve as an adequate starting point for study by students, interns and residents. Because of the limited space allotted to the various topics, however, it will probably be less useful to the practicing surgeon.

JOSEPH S. CAREY, M.D.

\* \* \*

**THE CLINICAL APPROACH TO THE PATIENT**—William L. Morgan, Jr., M.D., Professor of Medicine, the University of Rochester, School of Medicine and Dentistry; George L. Engel, M.D., Professor of Psychiatry and Professor of Medicine, the University of Rochester, School of Medicine and Dentistry. Illustrated by Evelyn Lipman Engel. W. B. Saunders Company, West Washington Square, Philadelphia, Pa. (19105). 1969. 314 pages, \$9.75.

The book was designed to prepare the medical student for his first clinical encounter and is the product of experiences with an innovative general clerkship at the University of Rochester. It describes the doctor-patient relationship, the roles of patient and student on the teaching ward and the steps used to acquire, analyze and report clinical data. Noteworthy chapters deal with the methods involved in establishing a relationship with the patient and eliciting the history of his illness, and with the proper recording of clinical data. Technical aspects of the physical examination have been set aside but its flow and sequence are carefully described.

Thorough instruction in bedside techniques and in the process of diagnosis becomes increasingly important in the education of tomorrow's physicians as the scope of laboratory medicine and use of technical assistants in patient care expand. This concise and skillfully written book may replace hours of preceptorship for today's sophisticated student undertaking a condensed curriculum and abbreviated clerkships.

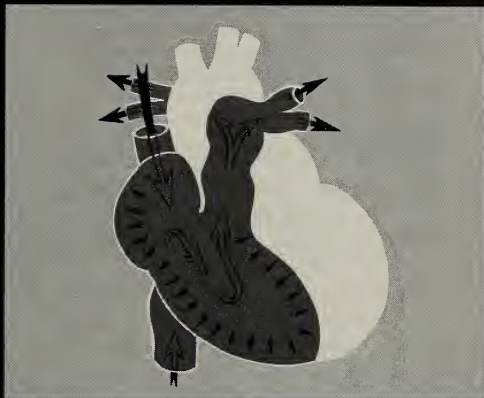
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\*Best, C. H. and Taylor, N. B.: *The Physiological Basis of Medical Practice*, 7th edition, Williams and Wilkins, Baltimore, 1961, p. 480.

# BOOKS RECEIVED

**CLINICAL CARDIOPULMONARY PHYSIOLOGY** (3rd Ed.)—Sponsored by the American College of Chest Physicians. Edited by Burgess L. Gordon, M.D., Visiting Professor of Medicine, Jefferson Medical College of Thomas Jefferson University, Philadelphia; Richard A. Carleton, M.D., Professor of Medicine, University of Illinois; Director, Cardio-respiratory Section, Presbyterian-St. Luke's Hospital, Chicago; and L. Penfield Faber, M.D., Clinical Associate Professor of Surgery, University of Illinois; Attending Thoracic Surgeon, Presbyterian-St. Luke's Hospital, Chicago. Grune & Stratton, Inc., 381 Park Avenue South, New York (10016), 1969. 754 pages, \$45.00.

**CLINICAL IMMUNOLOGY AND ALLERGY**—Leo H. Crip, M.D., Associate Professor of Clinical Medicine and formerly Chief of Allergy Clinic, School of Medicine, University of Pittsburgh; Director, Clinical Immunology Laboratory, Veterans Hospital; Consultant, Presbyterian-University and Montefiore Hospitals, Pittsburgh. Grune & Stratton, Inc., 381 Park Avenue South, New York (10016), 1969. 962 pages, \$35.50.

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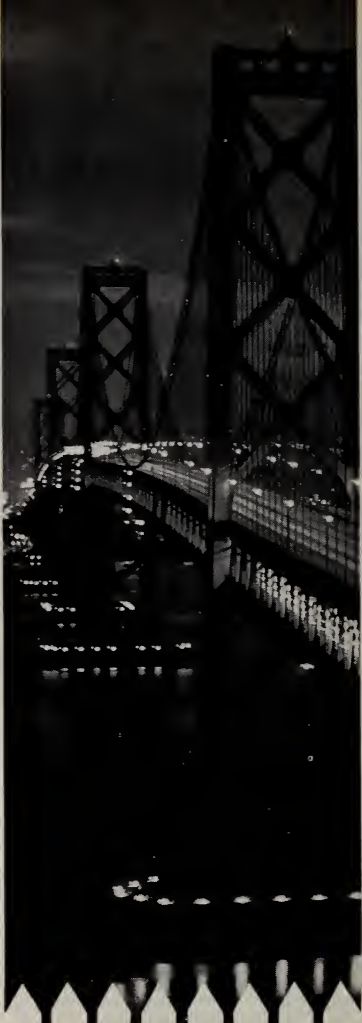
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# The Rhinoviruses of Man

MILAN FIALA, M.D., AND LUCIEN B. GUZE, M.D., *Los Angeles*

■ *Rhinoviruses, prominent agents of the common cold syndrome in man, are small ribonucleic acid (RNA) viruses resembling enteroviruses in their physicochemical properties except for high density and lability to acid pH. Rhinoviruses are propagated in human and monkey cells. Highest titers of virus are obtained in HeLa cell cultures. Rhinoviruses produce characteristic cytopathic effect in diploid fibroblasts. A plaque assay in HeLa cells is useful for their titration. The rhinovirus group includes many serotypes.*

*Although rhinoviruses cause predominantly upper respiratory tract symptoms, they may on occasion infect the lower respiratory tract. Volunteers with specific antibody, when challenged with homotypic rhinovirus, are protected against the common cold.*

SINCE THE 1930s the common cold has been thought, from results of human volunteer experiments, to be caused by a viral agent. Beginning in the 1950s reliable techniques were developed for the study of rhinoviruses, which are the major etiological agents causing the common cold. Using these techniques many antigenically different rhino-

viruses were isolated from patients with colds. A unifying concept of rhinoviruses emerged when all were found to be of small size (20 to 30 nm), to possess an RNA genome, to have a high buoyant density (1.4 to 1.42 grams per ml in CsCl), to be ether stable and pH 5.0 or 3.0 unstable.<sup>1-5</sup> Enteroviruses exhibit the same properties, except for high density and lability to acid pH, thereby allowing rhinoviruses and enteroviruses to be classified as separate subgroups of the larger picornavirus group.<sup>6</sup> Rhinoviruses are chiefly associated with upper respiratory tract disease, and can be isolated

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from the upper respiratory tract but not from the gut. Enteroviruses are responsible for nonrespiratory diseases (involving the central nervous system, gastrointestinal tract, skin, and cardiovascular system) as well as respiratory diseases<sup>7</sup> and can be isolated from the throat and the gut.

### Physical and Chemical Characteristics

Purification of rhinoviruses was achieved by propagating rhinoviruses in heteroploid cell cultures which grow rhinoviruses to high titers, followed by concentrating (taking advantage of the association of virus with cells at the time of harvest) and then purifying the virus with the use of fluorocarbon and density gradient centrifugation.<sup>3-5,8,9</sup> Continuous flow ultracentrifugation and isopycnic banding was used in another study<sup>10</sup> for the same purpose. Equilibrium sedimentation analysis in CsCl revealed a high density of rhinoviruses (1.4 to 1.42 grams per ml)<sup>3-5,9</sup> higher than other picornaviruses (1.32 to 1.36 grams per ml) except for foot-and-mouth disease virus (1.43 grams per ml). The high density of rhinoviruses might be due to its increased RNA content over that of acid-insensitive picornaviruses,<sup>8</sup> or to the accessibility of virus ribonucleic acid (RNA) to cesium ions which increase the hydrated density of the virus.<sup>10</sup>

Virus particles or its subunits were visualized by electron microscopy at two density levels in CsCl density gradients. The peak infectivity fractions with the density 1.40 grams per ml ("bottom component") contained particles 20 to 23 nm in diameter possessing icosahedral symmetry. Empty, noninfective particles were seen by electron microscopy in the density range 1.28 to 1.30 grams per ml.<sup>5</sup> A light "top component" (density 1.30 grams per ml) extracted from infected cells fixed complement with homotypic and heterotypic rhinovirus antisera.<sup>3</sup> Other investigators observed virus capsomeres 8 nm in diameter at a density of 1.28

grams per ml.<sup>10</sup> When rhinovirus infected cells were labeled with P<sup>32</sup> and the virus purified in a CsCl gradient, all radioactivity was confined to the peak-infectivity fractions of density 1.42 grams per ml.<sup>9</sup> Virus particles were observed in infected HeLa cells where, at later stages of infection and especially in the presence of increased Mg<sup>2+</sup>, they form cytoplasmic crystals displaying an hexagonal and rectangular lattice.<sup>11</sup>

The sedimentation coefficient of infectious rhinovirus type 2 has been determined as 155 S<sup>12</sup> and 155 S or 185 S, depending upon the assumed density of the virus particle.<sup>10</sup> Sedimentation coefficient of isotopically labeled rhinovirus type 2 was calculated at 143 S.<sup>9</sup>

No chemical analysis of rhinoviruses has yet been reported. Virus RNA has been studied relative to its infectivity,<sup>13,14</sup> its length as determined by electron microscopy<sup>8</sup> and its sedimentation properties in sucrose gradients.<sup>9</sup> Infectious rhinovirus RNA is extracted by phenol from infected cells and its assay facilitated by the use of DEAE-dextran. Rhinovirus ribonucleoprotein strands are twice as long as poliovirus strands. From their length the molecular weight of 4 x 10<sup>6</sup> daltons was calculated for rhinovirus RNA.<sup>8</sup> RNA extracted by phenol from purified rhinovirus sediments slowly as a heterogenous broad band and does not possess any infectivity.<sup>9</sup>

Rhinoviruses are best preserved at -70° C or lower but will maintain their titer for several days at 4° C and for at least an hour at room temperature. They are rapidly inactivated at 37° C or higher but at 56° C they are relatively more stable than enteroviruses.<sup>12</sup> RNA infectivity was inactivated at the same rate as virus at 35° C but was far more stable than virus infectivity at 50° C.<sup>15</sup> Characteristic properties of rhinoviruses include acid lability,<sup>1,16</sup> and ether or chloroform stability. The latter property indicates the absence of lipid from the capsid of the mature virion.

### Biological Properties

#### *Host Range*

Human rhinoviruses are isolated from nasal washings of patients with the common cold and very rarely from normal persons. Originally, rhinoviruses were isolated and propagated in roller tubes of monkey kidney cells at 35° C.<sup>17</sup> Subsequently, human kidney cultures were used under special conditions of lower than usual incubation

#### GLOSSARY

HeLa	..... A line of heteroploid cells
CsCl	..... Cesium chloride
nm	..... Nanometer (millimicron, 10 <sup>-9</sup> m)
Mg <sup>2+</sup>	..... Magnesium
S	..... Svedberg unit of sedimentation velocity
DEAE-dextran	..... Diethylaminoethyl-dextran
WI-38	..... A line of diploid human fibroblasts
PFU	..... Plaque-forming unit
TCID <sub>50</sub>	..... 50% infectious dose for tissue-culture

temperature (33° C) and at lower than customary pH (initial pH of 6.8 - 7.3), and under such conditions a greater variety of rhinoviruses was discovered.<sup>18</sup> Later, diploid fibroblast cell strains (especially W1-38 and other sensitive strains), in which rhinoviruses produce characteristic focal cytopathic effect, were found to be suitable for isolation of the majority of rhinoviruses.<sup>19</sup> More recently, ciliated cells of human embryonic nasal epithelium have been shown to be the best indicator for certain fastidious rhinoviruses.<sup>20</sup> For preparation of virus stocks with high titers, virus is propagated in heteroploid cell cultures such as M-HeLa cell culture in which titers of 10<sup>9</sup> PFU per ml are readily obtained.<sup>9</sup> Some rhinoviruses (so-called M-strains) can be propagated both in monkey kidney and human cells whereas other (so-called H-strains) can propagate only in human cells. Neither rhinoviruses nor their infectious RNA have reproduced in nonprimate cells which have been tested, such as L cells or chick-embryo fibroblasts.

#### *Virus Assay and Growth Cycle*

Initially, focal cytopathic lesions were used in a microplaque assay.<sup>21</sup> An end-point assay in tubes of diploid fibroblasts has been used most commonly for titration of virus and antibody.<sup>22</sup> A plaque assay has been developed in HeLa cells and, with some rhinovirus serotypes, is a superior assay of virus and antibody.<sup>23,24</sup> The plaque assay in HeLa cells was developed with the aid of increased (30 mM) magnesium and addition of DEAE-dextran to the overlay. Increased concentration of Mg<sup>2+</sup> enhances release of virus from cells and adsorption of virus<sup>25</sup> and also reduces the proportion of empty capsids in virus crystals.<sup>11</sup> The single step growth cycle of rhinovirus type 2 in HeLa cells has an eclipse phase of 6 hours and a latent period of 8 hours.<sup>25</sup> Virus replication is complete by 12 to 14 hours after infection. Virus RNA starts to be made at 5 hours after infection. Replication of rhinovirus in HeLa cells is very resistant to actinomycin D up to 10 micrograms per ml.<sup>9</sup> Synthesis of virus RNA occurs in the cytoplasm of infected cells as demonstrated by autoradiography.<sup>9</sup>

#### **Antigenic Characterization**

Many serologically distinct (as determined by neutralization tests) rhinoviruses have been isolated in every epidemiological investigation of the

common cold. In order to establish an international numbering scheme for rhinovirus serotypes, the National Institute of Allergy and Infectious Diseases and the World Health Organization compared rhinovirus "candidate" strains in neutralization tests against each other. Each strain had to be purified and satisfy the criteria set up for human rhinoviruses. Fifty-five distinct serotypes and one subtype were established.<sup>26</sup> Minor one-way crosses could be eliminated by absorption with human liver powder and were considered to be nonspecific. However, heterotypic antibody responses to eight rhinovirus serotypes were observed in human volunteers infected with types 13 and 16.<sup>27</sup> Heterotypic responses were also observed in patients with naturally acquired rhinovirus infections.<sup>28</sup> Serologic relationships among rhinoviruses were found using bovine antisera.<sup>29</sup> The problem of antigenic relationships among rhinoviruses should be explored further with a more sensitive test such as a plaque reduction test. As with some enteroviruses,<sup>30</sup> the presence of a persistent fraction and the breakthrough phenomenon in end-point neutralization tests with rhinoviruses may be due to aggregated virus.<sup>24</sup> The problem of antigenic stability of rhinoviruses after passage in the human nose has not yet been investigated.

#### **Genetics**

Guanidine resistant strains can be selected by picking virus from plaques of uninhibited size produced under overlay containing 100 micrograms per ml of guanidine. The frequency of these mutants is 10<sup>-3</sup>. Rhinoviruses propagate very poorly above 36° C, but it is possible to select temperature resistant strains by serial propagation at 38° C. No inhibitors for rhinoviruses were found in bovine sera, even in those sera strongly inhibitory to poliovirus.<sup>31</sup>

#### **Pathogenic Properties**

The prominent manifestation of rhinovirus infection is a common cold, as demonstrated when rhinoviruses are given to human volunteers.<sup>32</sup> Rhinovirus common colds in volunteers had a mean incubation period of 2.1 days and a duration of nine days.<sup>33</sup> In another volunteer experiment, two patterns of rhinovirus shedding and illness were recognized:

1. Early profuse shedding of virus with manifest rhinitis.

2. Late low level shedding usually without illness.<sup>34</sup>

Natural infection with rhinovirus carries a high risk of illness, about half of the infections being followed by respiratory illness.<sup>35</sup>

The naturally occurring syndrome of the common cold is clinically similar to other upper respiratory illness, but in the rhinovirus colds there is more frequent occurrence of rhinorrhea, nasal obstruction, sneezing, hoarseness and cough.<sup>36</sup> An increase in the neutrophil count in the blood is observed early in the course of the common cold in human volunteers.<sup>37</sup> Rhinoviruses are responsible for between 14 and 25 percent of acute respiratory illness in adults<sup>38-40</sup> with many types of rhinoviruses playing a role in one geographic area at the same time.<sup>40</sup> Rhinovirus infections are more common in certain periods of the year such as fall and spring.<sup>40</sup> In children rhinovirus infections are relatively less common, but the resulting disease may be more severe than in adults with fever and lower respiratory tract involvement.<sup>39</sup> In one study<sup>41</sup> rhinoviruses were isolated from children with lower respiratory tract disease in association with bacterial pathogens and it was suggested that rhinoviruses may predispose children to more serious bacterial infection. Other investigators<sup>42</sup> did not find an excess of rhinovirus infections in children with lower respiratory disease. Even in adult patients rhinoviruses, on occasion, infect the lower respiratory tract as evidenced by their isolation from sputum of chronic bronchitics. Rhinovirus infections may be related to exacerbations of bronchitis.<sup>43</sup> Lower respiratory tract can be infected if the virus is administered to volunteers by small particle aerosol.<sup>44</sup>

## Pathology

The pathologic changes of uncharacterized colds were studied by biopsy of the inferior conchus.<sup>45</sup> Edema of submucous tissue was followed by shedding of the surface epithelium which progressed to reach the deepest cell layers. The epithelium regenerated by the fourteenth day from onset.

## Rhinovirus Epidemiology

*Transmission.* Rhinoviruses are expelled by sneezing and coughing, and they infect man probably by attachment to cells of the nasal epithelium.<sup>46</sup> Rhinoviruses are generally considered ineffective in person-to-person spread<sup>47</sup> but some serotypes may spread extensively.<sup>48</sup>

*Environmental Factors.* Respiratory infections are more common in the cooler or rainy seasons. Available evidence suggests that factors such as low temperature, drop in temperature<sup>49</sup> or increased crowding are involved. This seasonal effect is thought not to be dependent on the enhancement of susceptibility to rhinoviruses due to exposure to cold temperature,<sup>50</sup> but rather on the increased transmission associated with greater production of nasal secretions in cold weather<sup>51</sup> and close contacts between people aggregated indoors.

## Immunity

Volunteers with preexistent serum antibody given rhinovirus inoculation intranasally usually have only modified infection or none at all.<sup>46,52</sup> Resistance to respiratory viruses, however, is now thought to be related more directly to antibodies in nasal secretions (chiefly IgA) than to serum antibodies (IgA, IgG and IgM).<sup>53</sup> This may explain why the correlation in volunteers of resistance with serum antibody is not absolute. No role of nasal or serum antibody in recovery from rhinovirus cold was noted.<sup>54</sup> The development of homotypic serum neutralizing antibody and immunity to rechallenge was surprisingly slow in one volunteer experiment, being maximal 6 to 12 months after experimental infection.<sup>55</sup> Another investigator noted the presence of neutralizing antibody at two weeks after experimental infection.<sup>56</sup>

In addition to specific protection against rhinovirus infection by antibody, some degree of non-specific resistance occurs beginning two weeks after infection<sup>57</sup> which is thought not to be due to interferon.<sup>58</sup> Rhinoviruses are, in cell culture, susceptible to inhibition by interferon. The degree of inhibition is somewhat variable in different laboratories depending on the virus strain and cell cultures used in the assay.<sup>59,60</sup>

Antibodies to different types of rhinoviruses are acquired throughout childhood and adolescence at different rates. This observation is consistent with the epidemiological behavior of rhinoviruses. Some serotypes appear in one geographic area only briefly during several years while other types produce small outbreaks (often several serotypes simultaneously) and then reappear two or three years later.<sup>40</sup> In natural rhinovirus infections, antibody rise occurs more frequently and to higher titers with M strains than H strains.<sup>22</sup> Rhinovirus neutralizing antibodies persist for years but they may decline sooner in the case of H strains.<sup>56</sup> Al-



though antibody induced by rhinovirus infection in man is usually strictly homotypic,<sup>61</sup> some heterotypic responses occur.<sup>27</sup> Successive colds in the same person are probably due to infection with a series of different rhinovirus serotypes.<sup>62</sup>

## Prophylaxis and Treatment Of Common Cold

At present vaccination appears impractical because of the very large numbers of rhinovirus serotypes and the narrow homotypic protection after intramuscular administration of killed rhinovirus vaccine.<sup>63,64</sup> Rhinovirus has been attenuated for humans by passage in diploid fibroblasts.<sup>65</sup> The spectrum of immunity following such live vaccine is as yet not known. Many laboratories are searching for synthetic compounds with inhibitory activity against respiratory viruses which would be useful for the treatment of the common cold.<sup>66</sup>

## Animal Model

Animal model of rhinovirus infection was developed in chimpanzees which upon intranasal and aerosol administration of 500 TCID<sub>50</sub> of type 14 or 10,000 TCID<sub>50</sub> of type 43 shed virus for a prolonged period and developed high levels of specific antibody. Clinical illness was not, however, observed.<sup>67</sup>

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## TREATMENT OF THE HYPERBILIRUBINEMIC INFANT

"Exchange transfusion continues to be the primary method of treatment and must be employed in any infant whose hyperbilirubinemia is secondary to hemolysis and whose bilirubin exceeds 20 milligrams percent. . . . Such infants must be carefully watched and given exchange at any time their bilirubin is under 20 milligrams percent, if signs suggestive of kernicterus appear. Light exposure with its relatively small lowering of bilirubin will have no place in such infants. How phenobarbital or Coramine® may help lessen hyperbilirubinemia in such infants remains to be seen. . . .

"The infant with hyperbilirubinemia which is nonhemolytic in origin is another story entirely. If the infant is full-term, the risk of kernicterus gets down to the level of the risk of exchange transfusion itself. We do not exchange such an infant unless signs suggestive of kernicterus, namely, deterioration of the Moro's reflex or the suck reflex appear. Such infants must be checked regularly and carefully by a physician who is experienced in evaluating these reflexes in the infant. Fever also is a sign of early kernicterus and must not be disregarded. . . . In such a full-term infant whose bilirubin is mounting, anything goes, I think; use of light and phenobarbital in small doses seem to be entirely justified. We flood the infants with water so that the bilirubin will look lower on the laboratory sheet. But we do not exchange a full-term nonhemolyzing hyperbilirubinemic infant, whether his bilirubin is 25, 30, 35, or 40; we've watched one go to 45, shivering and shaking, but nothing happened.

"In the premature infant without increased hemolysis, we use the figure of 25 milligrams percent of indirect bilirubin as the critical level, exchanging at a lower level, only if signs of kernicterus appear, that is, those early suggestive changes. Again in this type of baby, I think the use of a light cradle, fluids, and maybe a little phenobarbital appears entirely justified in order to avoid if at all possible the use of exchange transfusion."

—SYDNEY S. GELLIS, M.D., Boston

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# Some Psychiatric Comments on the Current Move Toward Sex Education Programs in the Schools

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THE DECLINE OF A consensus morality in modern times has made sex education more difficult and also even more critical for the development of functional adult personality patterns. Because of their own sexual inhibitions and uncertainties and their inability to adjust readily to changing values, in recent years parents have come to play a generally weaker role in moral and sexual education. Children have tended to hide behind the wall of silence that separates the generations and, with increasing frequency, are following the lure of early gratification into systems of conduct that prove in the long run to be unstable and inadequate. Because the moral revolution has produced rapidly mounting casualty lists, there has been a movement to fill the vacuum left by parental failure with full scale programs of sex education at all grade levels in the public schools.

The proponents of sex education, notably the nonprofit foundation SIECUS (Sex Education and Information Council of the United States), under the executive directorship of Mary S. Calderone, M.D.,<sup>1</sup> point rightfully to the fact that the growing child today is bombarded with lurid and unceasing messages about sex from his television set, from books and magazines and from the motion picture screen. Designed to arouse the ever-more-

jaded appetites of an increasingly sophisticated adult audience, these messages often outstrip the child's capacity to perceive clearly, hence result in confusion and overstimulation. The only way to combat this, say the sex educators, the only way to convey real and lasting moral values rather than the jazzed-up, anything goes standards of the take-it-all-off Noxema girl and *Playboy* magazine, is to introduce carefully designed, honest, informational programs at all age levels in the public schools. Only such a step can hope to stem the mounting tide of venereal disease and illegitimate pregnancy among the young.<sup>2</sup>

This is a compelling argument. There is no denying the hypersexuality of our culture, and the impression is very strong that the absence of a accepted code of conduct and the atmosphere of constant temptation has done irreparable harm to the minds and bodies of countless thousands. Furthermore, there is an undercurrent fear of the kind of moral change that is taking place in our country today. To many minds it is as if the whole structure of the American way of life is threatened. Periods of very rapid, not wholly rational change such as the present are difficult to live through. An era of change is always an era of anxiety. Old values are overthrown. There is nothing secure to be relied upon. Excesses occur and are hurtful, and some persons lose control altogether and become casualties of life. No one can be sure just where the process will lead, and there is a deep-seated uneasiness about life that is not easily tolerated.

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The present upsurge of interest in sex education programs is perhaps one manifestation of anxiety in a period of change. It is always a relief to find something apparently clear-cut to set to work upon. However, the problem of sex education is multifaceted and complex in its consequences. Indeed, so much is this the case that in the limited space of this paper the author will not in any way attempt a comprehensive review but rather will advance certain comments and considerations whose underlying thesis is precisely that the entire question of sex education in the schools is compound rather than simple and that, instead of being a matter to be dealt with just by aligning oneself on one side or another of the controversy, it is a problem that deserves careful delineation and continuing study by all those who are involved in working with the human personality.

Sex education programs deserve concerned and expert attention both as to their true effect upon the development of the individual and also with regard to their more far reaching influence on the structure and workings of society. The very nature and quality of personality itself are fundamentally related to the manner in which basic impulses like sex and aggression are managed. For example, the social changes set in motion by the sexual discoveries which Sigmund Freud first outlined in his "Three Essays on the Theory of Sexuality"<sup>3</sup> in 1905 have, in reality, created a new kind of man, who never existed before and who has problems and potentialities that we are only beginning to appreciate. Those fundamental concepts of the genetic and dynamic importance of the sexual life and of the role played by repression in the shaping of character have been incorporated into the very fabric of our culture and have altered for all time, with consequences still to be fully explored, our ways of raising children and the basic manner in which men and women relate to one another and conceive of themselves as sexual beings.

Now there are forces at work in education, in literature, in the performing arts, and in the evolving life styles of American youth that would seem to presage a still further reduction of the role of repression in sexual development. Those whose work affords them a window on the human soul must be attentive to processes like these in the

workings of society, and there is much to be thought through in terms of possible long-range consequences that such changes may engender.

## The Nature of Sex Education

In order to examine in more detail the matter of sex education programs, let us first inquire more carefully into the nature of sex education. What is it that needs to be taught and learned and why is it so critically important?

From the biological standpoint, sex education, of course, is largely superfluous. An animal that is in reasonable health and is free of man-induced fear will probably have little or no difficulty combining the promptings of instinct and the lessons of observation or the urgings of a more experienced mate into a reasonable approximation of the sex act the very first time out. An animal does not have to be taught in great detail how to do it; and, with a little practice, he soon becomes perfect in a skill that lasts him all his reproductive life.

Man is an animal too; and, if the successful completion of the sex act and reproduction were all that was at stake, he would be just as good at self-instruction as any other animal and there would be no need for anything like sex education. But of course man, with his prolonged period of immaturity and development, is also more than an animal, and sex is therefore a far more important matter for him. Because he can think, the human has gained a measure of independence from the demands of his body—from sex and hunger and aggression. Man is able to delay and divert the expression of urges that in lower animals are instinctual and imperative. He can, far more than other creatures, choose when and how and with whom or, indeed, if he will satisfy his physical desires. Because he can, man has been able to elaborate the patternings, the hows and whens and with-whoms, of his satisfactions into highly complex customs and practices that lend depth and character to his life and help to regulate relationships between human beings in his culture.

The sexual impulse can be thought of as energy. In the animal in his natural habitat it is discharged quickly. Its amplitude never becomes very great, and it is therefore not highly important. In man, however, the sexual impulse is amplified many times over by delayed discharge and by thought. Before any action occurs, each urge is processed through a complex set of moral conceptions hand-

ed down by society. Man thinks about whether to satisfy the urge now or wait and gain greater satisfaction later. He ponders what it will mean to him in the long run. He considers his conscience and weighs what other people will think of what he is contemplating doing. All of this is very complicated. Often people wish that they could be free of it; but it is out of these decisions that man makes, by himself, about his own impulses—out of hundreds of them, going on all the time and at all levels—that he builds his own personality. It is through this process of delay and consideration that the energy of instinct is transformed and magnified into a life force so that man becomes not just another animal but a striving, exploring, evolving, believing creature shaping his own future and controlling his own destiny.

And this, of course, is what sex education is most concerned with—not anatomy and how the act is accomplished, but the complex set of social understandings by which delay is accomplished and individual urges are transformed into great social institutions, like marriage and the family, that serve the historical goals of mankind. Humans try, in other words, to teach their children how to become a part of those institutions, how to contribute to them and to their continuing development, how to love, how to be true to themselves and constant in a relationship with another person, and how to care for their own children in turn.

## Current Problems in Moral And Sexual Education

The underlying difficulty in sex education as it is now practiced in the American home is that we are not at all sure what we are educating for. We are unwilling to stop just with the facts about sex, yet at the same time we are not at all certain where to go from there.

Sex education in the past, when chastity was the cornerstone of morality, was a finely balanced matter. In fact, it was probably somewhat hypocritical. The idea seems to have been to give children enough knowledge so that they would not be confused or misled by what they heard from companions but not so much that they would do something about it. In many of the older books, for instance, there seems to be an unwritten conspiracy to present the facts while at the same time avoiding two rather important things: one,

any mention of how sex is actually done and, two, the fact that it is sexy—that is to say, a source of pleasure. Consider, for example, the following quotation from the preface of a book written in the mid-1930s.<sup>4</sup>

Every topic from the symptoms of pregnancy to the workings of heredity is the outcome of [children's] searching minds, no more searching or acquisitive in regard to this subject than in regard to others—boat-racing, arctic exploring, deep-sea diving—but equally so. And the interest is as wholesome. Children are interested in the mechanics, the set-up, the laws of nature that bring human beings into the world. They are not interested (until later) in the emotional drives, conflicts, repressions, and adjustments that have grown up around the matter of reproduction. Briefly, they are interested in the origin of life—in themselves as human beings—not in sex.

The fear seems to have been that once the ancient secrets were out, children would throw themselves unrestrained into sexual activity, if not immediately, then certainly far sooner in adolescence than they should.

In point of fact, management of the sexual instincts in years past depended heavily on outright repression. Relatively few children found themselves exposed to even the rather restrained form of sex education then in vogue; and widespread ignorance of the basic facts combined with the classic inhibitory forces of childhood—shame, guilt and fear—to achieve a repressive influence more than powerful enough to deliver most young Americans to the marriage bed in a state of untutored virginity.

The difficulty now is that today's parents are too sophisticated and too humane to allow themselves any longer to manipulate the lives of their children through repression; yet, in part, they still long for the ends that repression once accomplished. They wish to educate, yet they are hesitant because they are not sure how to answer the children when they ask, naturally enough, what they are to do with what has been taught them. In fine, there is no clear-cut goal toward which the majority of parents can educate their children; and we have not yet evolved methods and attitudes of education that are suitable for a period of moral transition.

## Sex Education in the Schools

A number of specific concerns can be raised with regard to sex education programs in the



schools. For one thing, it is clear that the movement toward such programs is in large part a response to precisely the parental dilemma outlined above. Educators are concerned and highly professional people, but they are not concerned in the same way that parents are. It is easier for educators to supply facts and risk the consequences than it is for parents, with a far greater personal investment, to attempt the same thing with their own children. Yet it is hard to be sure that this lack of restraint on the part of the educator will prove beneficial in the end.

Schools by their very nature are required to deal with children in groups. Serious question might be raised as to whether such an approach is the most useful in a matter so individualized and so frequently fraught with conflict as sexual development. The question of timing is probably a critical one in sexual learning. Ideally, the most beneficial program would probably supply knowledge at approximately the same rate a normal child provides for himself when left to his own devices, a rate that delivers information just slightly less rapidly than curiosity and the need to know would seem to demand, so that the sense of wonderment and interest is never smothered by an overload of facts and yet the child is not left with an overwhelming void which can be filled only by the projection of his most primitive fantasies. Since school programs will perforce have to be adjusted to a hypothetical sense of what the average child knows and needs to know rather than to a specific awareness of where an individual child stands, they may well fall somewhat short of the ideal with regard to timing.

Then even today, sex is an area of conflict for many school children. As psychiatrists well know, learning in areas of conflict cannot be accomplished through didactic methods alone. Learners need to be given a sense of mastery over previously frightening ideas, as they are expressed and explored in the presence of others. Schools undoubtedly can provide such opportunities but the techniques are difficult and not ones in which they are customarily well versed. Furthermore, they do border on psychotherapeutic procedures and, to the degree to which they do so, are likely to tempt teachers away from the exercise of the traditional academic skills onto seemingly more glamorous but much more uncertain ground.

In meeting the need for open discussion, it would be unfortunate if schools were to overlook the child's concomitant need for privacy, an equally important aspect of sex education. Part of the sense of self is constructed over the years as the child struggles privately and repeatedly with subjects like sexuality, all by himself, before he is ready to share his thoughts with others. This fact should not be forgotten in the rush to force-feed sexual knowledge. Programs in sex education would do well to respect all of the child's needs and should allow him to maintain intact, whenever necessary, the boundary between his most secret thoughts and the rest of the world.

There is also some danger that programs of sex education in the schools may contribute to the already prevalent tendency to encourage children to grow up rapidly and to assume the trappings of adulthood before they are truly ready. Our society in the past has been characterized by the maintenance of a long period of childhood and adolescence. A young person is physically mature long before his intellect and personality become equipped for the complexities of function and interpersonal relationship that will be demanded of him in the adult world. Some writers have pointed to this lag as the cause of the high degree of adolescent turmoil that exists in our society, but psychiatrists have also understood it as a period not just of impatient waiting but of vital development, permitting a kind of refinement and development of personality not possible in cultures where responsibilities are shouldered as soon as the body is capable.

The essence of the adolescent opportunity is the chance to experiment with many different identities and ways of doing things before commitment to a fixed life style becomes necessary. It is out of this opportunity that the richness of adult personality is elaborated, yet one of the most characteristic features of contemporary middle class life is precisely the truncation of this period of sheltered adolescent trial, which retains the opportunity for repeated return to a relationship with the parents and does not too quickly require the hardening of personality.

There are many roots to our modern tendency to foreshorten the adolescent experience and many consequences. But in the area of sexuality, one cannot help wondering if the complex business of



transferring Oedipal feelings, with all of their shadings and nuances, outward from parent to a peer outside the family is really best accomplished by the sudden thrust into full experience that is likely to occur today. If sex education programs in the schools foster the trend toward precocity, they may inadvertently contribute to a simplification and constriction of personality that will be unfortunate in the long run.

### Sex Education Programs and the Process of Social Change

All the foregoing comments refer primarily to concerns about how well a school might be able to accomplish the task of sex education and to factors in the school situation that might make that task difficult. There are other crucial questions that might also be considered here—questions related to the age at which sex education might best be begun, the pace at which it should proceed, and the content of the instructional materials by which it is to be accomplished. But the truth of the matter is that most of these difficulties could be overcome readily enough in an enlightened program that utilized skilled teachers and adequate medical consultation. Furthermore, whether or not it is reasonable to expect our overburdened and embattled schools to be able to muster such skill and enlightenment, these are perhaps not the issues of greatest concern in regard to sex education. Of more moment is the whole question of the direction in which many current changes, including the so-called revolution in sexual morality, may be taking us. This seems a question that merits much closer study than it is likely to receive at the hands of school authorities busy with the problems of designing a curriculum and mounting a successful program.

The real challenge before all education today, be it in the home or church or school, is the challenge of preparing children for a changing world. We live in an era of moral exploration. We are literally creating a new kind of man. The old standards were based on religious teachings that are not now so widely followed. They were rooted in concepts of masculine superiority and property rights that have altered considerably over the years. Woman is no longer man's chattel. She is a person in her own right and new ideas are developing to further define the kind of person she can become.

New conditions in the world allow for new formulations. Widely available, simple methods of birth control are the most obvious, but there are others that are equally important at a deeper social level. Our growing affluence and its effect on feelings about property and possessiveness have altered some of our concepts about human relationships that were based on the idea of one person, a child or a wife, belonging to another. The increased crowding now occurring in our cities and suburbs has forced upon us a need to find ways to regulating relationships that will permit people to get along in much closer contact with much larger numbers of their fellow human beings. The growth of leisure time and the importance of pleasurable activities has tended to accent the importance of sexuality in our culture. At the same time there has been a continued decline of the importance of physical strength and combative ability. Since it was on strength that the institution of male superiority was for so many centuries based, this has produced far-reaching alterations in the nature of the relationship between the sexes.

Moral change occurs for many different reasons. The pressure of outside events, things like "the pill" or wars or increases in population, are frequent initiators of sweeping social change. Then there is often too a pursuit of change for its own sake, a search for newness, for novel ideas with which to identify. Also each generation, in its early years of greatest sexual power, before it has settled into an established pattern of expression, is likely to press for change as part of its rebellion against the adult world and in an effort to gain a greater measure of freedom from restrictions and restraints. Finally, change may occur simply because ideas and principles have a way of literally wearing out. Generations pass and the situations out of which the ideas and principles originally arose are forgotten. They come to exist only as dogma and do not have real meaning for those who have not contributed to their formulation and must therefore seek meaning for themselves in fresh concepts.

Many of these factors are operative in the world today. It is a time of great change, not only in the moral systems by which we live but also in racial relations, economic structures, and political practices. We and our children have an opportunity to create a world of the future in which

man may truly enjoy the fulfillment of all his potential for a virtuous and creative life. However, there are dangers in any period of change. Once initiated, the process of change is often poorly controlled, gathering momentum and heading faster and faster toward some new equilibrium which often is quite different than that envisioned by those who began the process. Even now, for example, in the area of morals, although the world seems to stand on the threshold of what may be highly significant developments in the management of sexual instincts and feelings, we cannot be at all sure where the end will lie.

There is opportunity here, opportunity to conserve what is best of the past and to add from what is new in the present to create a system within which man may be both responsible and also free to a degree which he has never before attained. But there is danger too, the danger of a new suppressive orthodoxy emerging to take the place of old doctrines, or the danger inherent in the unpredictable effects of alterations in cultural patterns of repression and satisfaction of impulses. Traditionally we have been a society which has allowed a good deal of aggressive expression and has inhibited sexuality. In our overcrowded world, that pattern is no longer serviceable; and we are shifting rapidly, with unknown consequences, to one diametrically opposed, which inhibits fighting and encourages sexual thought and experience. It would seem imperative that psychiatry and the behavioral sciences begin to investigate what some of the effects of such basic shifts may be on personality development.

It may well be that in many of the things it is currently involved in, including the mounting of programs of sex education, the adult world is responding to motivations that are not altogether conscious. One senses that today's adults may, in fact, be educating children to be their agents of change. Adults are themselves in many instances dissatisfied with the old order and the old morality, but they do not know how to alter things and perhaps would not dare to do so if they did. Hence they seem to prefer to leave the question to the tides of the future and content themselves with setting the process of change in motion by educating their children. But the opportunity to change is too precious a responsibility to be entrusted wholly to young people and to largely irrational forces. The whole question of personality and instinct control calls for professional study;

and sex education is most needed among adults who for the space of this generation are charged with the care of the world and who, with help, might be able to find new directions that would be evolutionary rather than regressive.

## Responsibility for Sex Education

Finally, a word might be said about the apparent conflict between those who advocate sex education in the schools and those who would retain that process within the home. It is plain to see that we need greater honesty and wisdom in the means by which we transmit information and attitudes regarding sexuality to the young. As the institution traditionally charged with cultural knowledge and values to succeeding generations, the educational system, despite its recent difficulties, is a reasonable place to begin the attempt to upgrade sexual learning.

It will, of course, be helpful if the schools can keep clearly in mind the fact that the material they are dealing with is of an entirely different order of emotional importance than their more customary subject matter. Thus, moderation in approach and the judicious use of expert consultation around questions of timing and content are likely to enhance the effectiveness of their efforts in this highly charged area. It will also be helpful, however, if parents can manage to reverse their recent tendency to abandon altogether to the school the responsibility for functions that in the past have been carried out by the family.

Sex education in the schools does not exclude sex education in the home. Properly used it can stimulate and enhance learning within the family, and the family in turn may compensate for some of the deficiencies of the group-oriented and more impersonal kinds of teaching which may be necessary in the school. In other words, perhaps in the area of sexuality parents and educators might rediscover the fact that school and home are fundamentally interdependent and that one does not function well without the other.

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# A Graphic Guide for Clinical Management of Latent Syphilis

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■ *A graphic luetic record form is used as a guide to physicians in diagnosis and management of latent syphilis. The form provides a uniform method of recording laboratory and clinical findings as well as treatment. It facilitates checking progress and forwarding of information necessary to assure continuity in treatment of patients with latent syphilis who are transferred to other medical facilities. It is designed primarily as a guide to the clinician who does not specialize in the treatment of syphilis.*

LATENT SYPHILIS, the quiescent stage during which clinical signs or symptoms of the disease are lacking, always has presented special problems in diagnosis and management. While the treponemicidal antibiotics have simplified treatment, misuse of them has aggravated these problems. In addition, the development of more specific serologic tests has refined accuracy, but also has complicated laboratory diagnosis. The physician today needs to be more aware of these problems and must be better informed regarding the laboratory procedures used. This paper presents a graphic guide to the clinician for diagnosis and treatment of latent syphilis.

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The advent of treponemicidal antibiotics has shifted the concern of the physician from treatment to diagnosis. Indications are that, far from eradicating syphilis, these antibiotics are driving the disease underground and increasing the difficulty of detection.<sup>1</sup> Although the incidence of the disease has more than trebled since 1955, the chancre and the secondary rash no longer are commonly seen. Undoubtedly, some of these lesions are being suppressed and the disease masked by the indiscriminate use of antibiotics. It is difficult otherwise to explain the predominance of latent syphilis in current medical practice. The ominous prospect of a widespread resurgence of the disease in its tertiary forms looms ahead.

In the absence of clinical signs or symptoms of the disease, the physician is dependent upon the laboratory for diagnosis. The nontreponemal tests for syphilis are no longer adequate for this purpose. Of the dozens of these tests devised, only a few remain in use today. In most laboratories nowadays the Venereal Disease Research Laboratory



(VDRL) slide test is used as a screening procedure for syphilis. This is a nontreponemal flocculation test for detecting the presence of reagin in the patient's serum. The antigen consists of a suspension of cardiolipin-lecithin prepared from purified beef heart extract. Reagin in the blood of patients who have or have had syphilis, when mixed with this suspension, precipitates the antigen. The relative amount of reagin present is measured by serial dilutions of the patient's serum.

Laboratory diagnosis, however, in the absence of clinical signs of syphilis, is dependent on demonstrating the presence of treponemal antibodies in the blood. Because of the time and expense involved in performing tests to detect these specific antibodies, their use by public health laboratories is controlled. Before performing treponemal antibody tests, the California State Public Health Laboratory usually requires that a preliminary VDRL test must have been done. A specified time-sequence schedule in requesting laboratory tests needs to be followed by the clinician in order to meet laboratory requirements. The physician inexperienced in these prerequisites for the processing of serologic specimens often is confused.

The authors have devised a Luetic Record Form, and instructions for using it, to guide the physician in serologic testing of patients. This form has been in use in institutions of the California State Department of Corrections for the past two years and has proved useful in maintaining continuity of treatment in a mobile population. It is oriented primarily toward definitive diagnosis and management of both early and late latent syphilis. Its graphic design serves as a flow sheet which facilitates keeping record of progress and treatment. Emphasis has been placed on adherence to the time-sequence relationships required in requesting serologic tests. (See pages 16 and 17.)

A Luetic Record is filled out for a patient when a "Reactive" or "Weak Reactive" VDRL report is received from the laboratory. At this time, inquiry by the physician should be made regarding previous history of the disease. Previous records are requested, including last serologic test results and treatment. These data are entered in the top titer-treatment box and under "Remarks." A complete physical examination, including darkfield study of any suspicious lesion, must be made and epidemiological data obtained. Positive findings should be entered under "Remarks." The schedule of

follow-up tests is then carried out as noted in the graph.

## Discussion

**VDRL Test:** The VDRL should precede the performance of more specific tests. This test is not specific for syphilis. Recent or concurrent illnesses, vaccinations, immunizations, heroin addiction, lupus erythematosus, lymphoma, and other non-luetic diseases or conditions may produce false-positive reactions. Roxas and Associates of St. Louis report an incidence of 33 percent false-positive results of VDRL tests as determined by negative confirmation with the FTA-ABS.<sup>2</sup> In men confined at the California Institution for Men, a state penal institution at Chino, California, the incidence of false-positive VDRL tests, similarly determined, was 64.3 percent. At the California Institution for Women, a state penal institution at Frontera, California, the incidence was 42.5 percent. This higher incidence of false-positive VDRL tests among inmates in these institutions is considered related to the high percentage of heroin users in these groups. Accordingly, a reactive VDRL alone, in the absence of other evidence of the disease, should not be the basis for diagnosis or treatment of syphilis. On the other hand, a negative VDRL does not necessarily exclude syphilis. The laboratory cannot substitute for clinical judgment and experience.

**FTA Tests:** Of the treponemal antibody tests, the Fluorescent Treponemal Antibody test (FTA) has shown great specificity. An absorption technique devised by Hunter et al removes nonspecific treponemal antibodies from human serum before testing and increases the sensitivity of the FTA test.<sup>3</sup> It is then referred to as the Fluorescent Treponemal Antibody Absorption (FTA-ABS) test. In this test, a slide containing dried *Treponema pallidum* is covered with the patient's blood serum. Antibodies for syphilis, when present in the globulin fraction of the serum, attach to the treponemes. Separately prepared fluorescein-tagged antibodies to human globulin are then overlaid on the slide. The globulin attached to the treponemes now acts as an antigen to bind the fluorescein-tagged globulin antibody. Fluorescence of the treponemes thus reveals the presence of treponemal antibodies in the patient's serum and the test is reported as "Reactive." The FTA-ABS is employed by most laboratories today. Accordingly, the FTA shown

on the graph should be interpreted as FTA-ABS unless otherwise indicated by the laboratory report.

**TPI Test:** The Treponema Pallidum Immobilization (TPI) test involves testing the patient's serum for antibodies against live Treponema pallidum. Because of the complexity and expense involved, use of the TPI is restricted to patients in whom a diagnosis cannot be resolved by use of the FTA-ABS alone. The TPI test ordinarily is restricted by the California State Department of Public Health to individuals who fall in the following groups: (1) Patients in whom the VDRL has been reactive for at least three months before request for treponemal test and in whom there is no clinical or historical evidence of syphilis; (2) patients with non-reactive standard (VDRL) tests who show clinical evidence suggestive of syphilis; (3) pregnant women without evidence of syphilis and having at least one reactive VDRL.<sup>4</sup> When the TPI test is justified, additional laboratory requirements need to be met.<sup>5</sup> The patient must not have received injected antibiotics within one month, nor oral antibiotics within one week of obtaining the blood specimen. Special care must be observed in the preparation of equipment for drawing blood. Rubber-stoppered vials must not be used. Shipment of specimens should be made in containers provided by the Public Health Laboratory and be accompanied by a clinical data sheet.<sup>6</sup> (TPI containers are available from most local health departments in California.)

**Titration:** The VDRL test is of value in measuring the degree of antibody reaction to syphilis in the body and may reflect response to treatment. However, comparison of post-treatment titers with pre-treatment titers as a measure of persistence of infection is of questionable value in latent luetics. The titers should be checked periodically, nevertheless, as reacquired syphilis is always a possibility. Only a minimum change in titer of two dilutions is considered significant. Evidence at present indicates that the FTA-ABS will not be useful in evaluating the degree of infection or response to treatment. VDRL titration is the only laboratory procedure now available for such serologic evaluation and should be obtained in each case before initiating treatment to provide a basis for future comparison. However, it should not be the sole criterion for further treatment.

**Spinal Fluid Examination:** A spinal fluid examination is considered essential for the diagnosis of

latent syphilis.\* It is mandatory in late latent syphilis in order to exclude asymptomatic neurosyphilis. At least one spinal fluid examination should be done in every case of latent syphilis before treatment is terminated. Where neurosyphilis is diagnosed, the spinal fluid examination should be repeated in three months after completion of each course of treatment. In interpreting the spinal fluid examination findings, the following results are significant: a cell count done immediately after a blood-free spinal tap showing more than four lymphocytes; total protein of more than 40 mg per 100 ml; a reactive VDRL.<sup>7</sup> Titration of a reactive VDRL should be obtained. In contrast to blood serum, a false-positive reactive VDRL in spinal fluid is rare.

**Diagnosis:** In differential diagnosis between early latent and late latent syphilis, the two-year period without signs or symptoms of this disease, as specified by the California State Department of Public Health in its Confidential Morbidity Report (Form 243-102), has been followed by the authors. However, this is arbitrary. The World Health Organization divides early latent and late latent syphilis stages at four years.<sup>8</sup>

**Treatment:** Antibiotics have supplanted all previous agents in treatment. After 26 years, penicillin, given parenterally, remains the antibiotic of choice. The importance of adequate duration as well as intensity of treatment with this antibiotic cannot be overemphasized. Anyone who has watched the spirochete of syphilis moving actively in a concentrated solution of penicillin for hours under the microscope cannot help being impressed with the importance of the time factor in destroying the organism. Recent reports by Smith and others of the detection of live spirochetes in patients with latent syphilis after treatment with apparently adequate doses of penicillin further suggest the importance of duration as well as intensity.<sup>9</sup> Optimal treatment of latent syphilis as recommended by the U.S. Public Health Service is quoted herewith as a general guide<sup>7</sup>:

With non-reactive spinal fluid examination:

Rx: Benzathine Penicillin G: (Bicillin, Permapen) 2.4 million units total by intramuscular injection at one clinic session.

Without spinal fluid examination:

Rx: Benzathine Penicillin G: (Bicillin, Per-

\*Some clinicians withhold doing a spinal fluid examination on patients with early latent syphilis before treatment and arbitrarily refrain from doing such test on these patients who are under 40 years of age, until after treatment is completed.

PEREYRA-VOLLER LUETIC RECORD FORM

	Date	O/W	2	4	8	16	32	64	FTA	Medication
<b>PREVIOUS VDRL/FTA</b>										
VDRL R W										<b>DRUG SENSITIVITIES</b>
FTA										<b>REMARKS</b>
R NEG W										
Wait 2 weeks										
FTA										
R NEG W										
Wait 2 months										
TPI										
R NEG W										
Spinal										VDRL: WBC: Protein:
<b>First Treatment</b>	Medication: _____ M. D.									
Wait 3 months	Started: _____ Ended: _____ R. N.									
VDRL										
NEG. R W										
IF SAME OR LOWER TITER, NO FURTHER Rx										
HIGHER TITER										
<b>Second Treatment</b>	Medication: _____ M. D.									
Wait 3 months	Started: _____ Ended: _____ R. N.									
VDRL										
NEG. R W										
SPINAL										VDRL: WBC: Protein:
<b>Third Treatment</b>	Medication: _____ M. D.									
	Started: _____ Ended: _____ R. N.									
<b>DIAGNOSIS:</b>	Primary ( ) Secondary ( ) Early Latent ( ) Late Latent ( )									
Other _____	Reported to Health Department _____ Date _____ M. D.									
Name: _____	No. _____ Birth Date _____									



# INSTRUCTIONS FOR USE OF PEREYRA-VOLLER LUETIC RECORD FORM

## PROCEDURE

## RECORDING

### VDRL TEST

1. Serologic test reported VDRL "Reactive or "Weak".
  1. Open Luetic Record Form as follows:
    - a. Enter name, number and birth date of patient at bottom of form.
    - b. Circle VDRL R or W at top left of form.
    - c. Enter date of test in 1st space to right of VDRL R W.
    - d. Enter VDRL titer in succeeding squares in 2nd titer block, if reported.
    - e. If previously investigated, obtain prior VDRL/FTA, date of tests, titer and treatment. Enter data in 1st titer block at top of form.
    - f. Check appropriate diagnosis at bottom of form.  
Record date reported to Public Health Dept.
    - g. List antibiotic drug sensitivities under DRUG SENSITIVITIES at top right of form.
  2. Enter date blood drawn for FTA in 1st square of 3rd titer box
2. Submit 5cc of blood to laboratory. Request FTA test.
3. First FTA reported "R". (VDRL may be reported by laboratory together with FTA test requested).
4. Begin First Treatment - OR -
5. Do SPINAL fluid examination. Then give First Treatment.
6. First FTA reported "NEG".
7. First FTA reported "W". Wait 2 weeks, then submit 5cc of blood to laboratory. Request repeat FTA.
8. Second FTA test reported "R". Treat - proceed as under No. 4 or No. 5 above.
9. Second FTA test reported "NEG".
10. Second FTA test reported "W". Wait two (2) months, fill out required forms and submit 10cc of blood to laboratory with request for TPI test.

### FIRST FTA TEST

3. Circle R below 1st FTA. Enter VDRL titer in 3rd titer box, if reported.
4. Circle FIRST TREATMENT. Enter medication ordered. Clinician initials order. Show date treatment STARTED and ENDED. Nurse initials on completion of treatment.
5. Circle SPINAL. Enter date and results of spinal fluid examination to right of SPINAL. Then proceed as under No. 4 above.
6. Circle NEG below 1st FTA. Enter "No further observation or treatment indicated" under REMARKS. Clinician signs order.
7. Circle 2nd FTA. Enter date blood drawn for 2nd FTA in 1st square of 4th titer box.

### SECOND FTA TEST

8. Circle 2nd R to left of 2nd FTA. Enter VDRL titer in 4th titer box, if reported.
9. Proceed as under No. 6 above.
10. Circle W below 2nd FTA. Circle TPI. Enter date blood drawn for TPI test in 1st square of 5th titer box.

### TPI TEST

11. TPI test reported "NEG".
12. TPI test reported "R" or "W". Treat - proceed as under No. 4 or No. 5.
11. Circle 3rd NEG then proceed as under No. 6 above.
12. Circle R or W below TPI. Enter VDRL titer in 5th titer box, if reported. Make entries as under No. 4 or No. 5 above.

Explanations: The graph on the obverse conforms to time-sequence schedules for serologic testing of California State Public Health Laboratories. The PROCEDURES listed above should be correlated with their numerical equivalents under RECORDING.

Definitions: FTA -- Fluorescent Treponemal Antibody Absorption test.

TPI -- Treponema Pallidum Immobilization test.

VDRL -- Venereal Disease Research Laboratory nontreponemal antigen test.

Diagnosis: Primary -- chancre present, serology positive or negative.

Secondary -- skin, mucosal or other general manifestations present.

Early Latent -- asymptomatic infection of less than two years duration.

Late latent -- asymptomatic infection of two or more years duration.

Other -- Specify type, e. g., Neurosyphilis, Cardiovascular, Congenital.

mapen) 6.0 million units intramuscularly, total.

Initial injection 3.0 million units

Then 1.5 million units at 7 and 14 days after initial injection.

Or: PAM (Procaine Penicillin G with 2 percent aluminum monostearate): (Depo-Penicillin, Lentopen, Wycillin)

4.8 million units total by intramuscular injection.

2.4 million units initial injection

1.2 million units in each of two subsequent injections three days apart

Or: Aqueous Procaine Penicillin G:

4.8 million units total by intramuscular injection

600,000 units daily for eight days

When penicillin is contraindicated, oral Tetracycline or Erythromycin, in 250 mg capsules is recommended, as follows:

Tetracycline or Erythromycin 30 to 40 grams in 10 to 15 days, as follows:

1,000 mgm (four capsules) four times daily.

In neurosyphilis, cardiovascular syphilis and late benign syphilis, treatment should be more intense and more prolonged. Three million units of benzathine penicillin G should be given at weekly intervals for three doses or a total of nine million units. For further information regarding treatment, the U.S. Public Health Service Publication number 1660 of January 1968, entitled "Syphilis, A Synopsis," should be consulted.

Stereotyped treatment, however, has no place in the management of syphilis. Therapy must be individualized. This is true particularly in the management of late latent syphilis. Not only is the duration of treatment important, but also the avenue of penicillin administration may be crucial in assuring efficacy of treatment in these patients. While the mucocutaneous lesions of early syphilis can be eradicated readily even by orally administered treponemicidal antibiotics, the destruction of spirochetes in some of the internal less vascular tissues of the body in patients with the late latent disease may not be accomplished even by intramuscularly administered antibiotic. In such patients, sometimes only continuous massive intravenous penicillin therapy can provide the high concentration of penicillin in the blood necessary to penetrate and sustain treponemicidal levels of the antibiotic in these relatively avascular tissues.

**Morbidity:** Syphilis is a reportable communicable disease. The reporting of patients serves the dual purpose of giving information for contact investigation to prevent further spread and of providing statistical data for determining prev-

alence of the disease. Because of the illicit avenues of transmission and the social stigma attached to syphilis, private physicians often are constrained in exposing patients to investigation. In consequence, according to Webster<sup>10</sup> nine out of ten patients with syphilis are not reported. Even though recognizing the importance of immediate treatment of patients with infectious syphilis and the need to investigate the source of infection, the average physician today is not seeing or not recognizing the disease at that early stage.<sup>1</sup> The majority of syphilitic patients reported have latent disease and have little knowledge or recollection of the source of their infection. Hence, the tenuity of epidemiological investigations.

Statistics obtained from eight major cities in the United States confirm the preponderance of latent syphilis in the population.<sup>11</sup> The number of infectious cases reported in 1968 by these cities was 2,843 or 26 percent, while the patients reported with latent syphilis totaled 8,082 or 74 percent. According to Webster, these figures would have to be multiplied by ten to include the total number of patients with syphilis treated but unreported by physicians. How many remain unrecognized and nonspecifically treated in this hit-and-run antibiotic age can only be conjectured. The routine serologic screening of selected groups, such as county hospital patients, inmates of correctional institutions and prisons, migrant labor populations would appear indicated. This should be facilitated by automation such as the recently introduced ART (Automated Reagin Test for syphilis) system.<sup>12</sup>

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# CASE REPORTS

## Median Cerebrofacial Dysgenesis

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THE CONGENITAL CLEFT LIP deformity is usually considered a severe cosmetic defect, and there is general agreement that repair should be undertaken within the first several months of age. Particularly if the deformity is not bilateral (or "double") the prognosis is generally good, and usually there are no other severe deformities associated with the condition. The rare midline cleft lip, however, is often accompanied by severe brain dysgenesis, and it is therefore most important to recognize these cases of arhinencephalia, for the patient is likely not to survive infancy.

To those familiar with the syndrome, children with midline cleft lip and palate present an easily recognized and characteristic appearance. Although cases of this kind are sporadic in occurrence, they are of sufficient frequency to justify an awareness of their quite typical clinical course. Complex interrelationships between the patient and his family demand of the attending physician a knowledge of the patient's capacity for development, the likelihood of recurrence in the family, and a reasoned approach to therapy. The following case underscores these considerations.

### Report of a Case

The patient, a 2.08 kg boy, was born to a 30-year-old gravida 8 para 8 woman at 37 weeks of gestation. Arhinencephaly was diagnosed at birth.

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Review of the pregnancy showed no complications. Family history included diabetes mellitus. Two of the patient's siblings had died of nausea, vomiting and dehydration, one at 8 months and the other at 18 months of age.

At birth the patient showed a wide midline complete cleft of the lip, alveolar ridge and palate, and absence of the prolabium, columella, premaxilla and nasal septum. There were no evident extracranial anomalies except undescended testes and a small penis. X-ray films of the skull showed midline defects of the sphenoid and maxillary bones, hypotelorism and absence of nasal bones.

Within the first month of life, the patient was noted to have apneic spells, for which phenobarbital was given. He was discharged at 29 days weighing 5 pounds 13 ounces. He did poorly at home and at age 7 months was put into hospital for pneumonia. He had only gained 1 pound 3 ounces in the first 6 months of life, although the mother obviously loved the child very much and was taking excellent care of him.

Because of the attention focused on this child by the family and their dissatisfaction with gavage feedings, he was readmitted at 8 months for repair of the cleft lip. At this time he was hydrocephalic and he had a high-pitched cry. Through the anterior fontanel, which was 6 cm wide, intracranial contents were bulging. The head transilluminated brilliantly (Figure 1). The patient lay motionless with no prehensile capability, with occasional weak active movements, and with increased tone in all extremities. Generally hyperactive stretch responses were noted and Babinski's sign was evoked bilaterally. He reacted to noxious stimuli only. Cranial nerve examination revealed unequal and poorly reactive pupils, horizontal and vertical nystagmoid movements at rest, absence of doll's-eye responses, and bilateral deafness. An electroencephalogram showed diffuse excessive background slowing. No spinal fluid abnormality was noted. A ventriculogram showed only a thin mantle of cerebral cortex, a large single ventricle, and non-communicating hydrocephalus. Chromosome studies, done twice, showed a normal karyotype.





Figure 1.—Photograph showing transillumination of the head.

To enable the parents to feed the child more satisfactorily and to improve his appearance, a straight-line closure of the midline cleft lip was done at 8 months. There were no complications of anesthesia. The patient's temperature was carefully monitored during the procedure, a large silk suture was placed in the tongue and traction was placed on it on several occasions in the postoperative period to relieve obstruction of the upper airway. The wound healed without complication and the patient was discharged on the tenth day. He was able to suck from a premature infant nipple, and improvement in appearance made him more acceptable within the family. Suddenly at age 9 months his pulse rate slowed to 30 per minute and he died shortly thereafter.

At autopsy the brain, which weighed 200 grams, showed massive internal hydrocephalus. The cerebral cortex, 2 to 3 mm thick, was stretched into a thin undivided single ventricle or holosphere, which represented both lateral and third ventricles and communicated with the fourth ventricle by way of the patent cerebral aqueduct. Posteriorly, the ventricular cavity was roofed over by a thin membrane. Olfactory bulbs and tracts and cribriform plate of the ethmoid, corpus callosum, fornix, septum pellucidum, cerebral peduncles and medullary pyramids were conspicuously absent. Cranial nerves II to XII were identified. Anatomical diagnosis included alobar holoprosencephaly in association with a midline facial defect; hypoplasia of thymus, adrenals, testes, and pituitary; bi-lobed right lung with pulmonary conges-

tion; cardiac dilation and acute bronchial pneumonia.

## Comment

Although Rudius<sup>1</sup> first observed and recorded a description of similar conditions in 1588, not until 1882 did Kundrat identify the teratologic spectrum which extends by degrees from cyclopia, the most extreme example of midline face and brain anomaly, to the relatively mild absence of the corpus callosum.<sup>2,3,4</sup> Kundrat coined the term *arhinencephaly* because he felt that absence of the olfactory bulb and tract were the cardinal features of this disorder. It has been shown by Yakovlev<sup>5</sup> that the common denominator of these malformations is the failure of evagination of the secondary telencephalic vesicles and of cleavage of the prosencephalon. The supralimbic frontal lobes in front of the gigantopyramidal cortex fail to develop, the olfactory vesicles fail to evaginate and the prosencephalon fails to cleave. Therefore *Holoprosencephaly* has been advanced as a more accurate term than *arhinencephaly* for this malformation, inasmuch as not all rhinencephalic structures are absent.<sup>2</sup>

The typical appearance of median facial anomalies should immediately alert the clinician that dysgenetic intracranial states may coexist. Median cleft lip or bilateral cleft lip with absence of median philtrum and premaxilla and prolabium anlage, associated with orbital hypotelorism, flat nose, microcephaly and sometimes trigonocephaly together, signal the presence of holoprosencephaly with all its attendant implications for impairment of function and threat to life.<sup>3,6</sup> Thus the terms *median cleft lip*, *cebocephaly*, *ethmocephaly* and *cyclopia* describe variants of these median facial anomalies which are virtually pathognomic of holoprosencephaly.

It must be emphasized, however, that not all median facial anomalies reflect an underlying brain abnormality. Median cleft nose and median cleft prolabium and premaxilla may occur in combination with cranium bifidum occiput frontalis. Patients with this condition have orbital hypertelorism and, unlike those with midline facial anomalies associated with hypotelorism, are usually not retarded.<sup>7</sup>

When holoprosencephaly occurs with extra-cephalic abnormalities, the literature suggests the affected patient is likely to have 13-15 ( $D_1$ ) trisomy.<sup>8,9</sup> This trisomy state, first reported in 1960,

may include cardiac anomalies, abdominal visceral abnormalities, anomalies of the hands, feet and skin, in association with cleft lip and palate, and holoprosencephaly. Although all patients with  $D_1$  trisomy are mentally retarded and all have gross cerebral defects,<sup>8</sup> not all have agenesis of the olfactory bulbs, tracts and trigone.<sup>9</sup> The likelihood of recurrence in the same family of both this trisomy state and normal karyotype holoprosencephaly is not yet known but is probably remote.

In holoprosencephaly apneic spells or seizures, intra- and extra-uterine growth retardation, poikilothermia, spasticity and deficient psychomotor progress are common. These physiological abnormalities together with the structural anomalies such as cleft lip and palate direct the course of therapy. Although patients with alobar holoprosencephaly usually die within the first year, others with less severe variants of this spectrum may have a normal life expectancy.

Diagnosis is based on a careful general examination which includes transillumination of the calvaria (Figure 1). Patients with classical alobar holoprosencephaly have characteristic facies (Figure 2). If orbital hypotelorism and trigonocephaly are demonstrated on skull films, defects of the rhinencephalon and forebrain are probable. Pneumoencephalography shows a large single holosphere which represents common lateral and third ventricles. Chromosome studies occasionally show abnormalities.

Therapeutic efforts beyond the attempt to maintain body temperature and nutrition depend on parental attitudes. Where forces of parental love are compelling, efforts to facilitate feeding and to improve the infant's appearance by repair of the median cleft of lip and palate seem indicated. Surgical repair must be done only with full understanding of the overall prognosis for the infant. These considerations dictated operative intervention in the case here reported.

## Summary

A case of alobar holoprosencephaly is described and nosological, embryological, diagnostic and

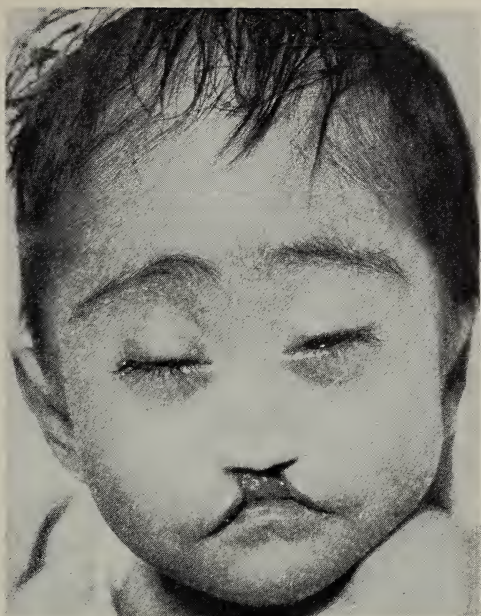


Figure 2.— Typical appearance of patient with alobar holoprosencephaly.

therapeutic implications are reviewed. Surgical correction of facial defects, decried as futile by some physicians, may well facilitate care of infants with this condition in certain circumstances.

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# Secondary Syphilis Misdiagnosed as Lymphoma

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IN 1968 SYMMERS reviewed the histologic material of 600 patients with an initial biopsy diagnosis of Hodgkin's disease and found that three of the patients actually had either primary or tertiary syphilis as the correct diagnosis.<sup>1</sup> However, 25 years have elapsed since the generalized lymphadenopathy of secondary syphilis was last reported to have been misdiagnosed as one of the lymphomas, in particular giant follicle lymphoma.<sup>2</sup>

Since 1944 a new generation of physicians has been trained, some of whom have never seen a case of secondary syphilis. Therefore, attention is again called to the fact that syphilis is still a common disease that should be considered in the differential diagnosis of generalized lymphadenopathy. This report describes two patients seen recently, both of whom had syphilis, misdiagnosed in one case as giant follicle lymphoma and in the other confused with Hodgkin's disease.

## Report of First Case

*Case 1.* A 31-year-old Negro man noted tender right inguinal lymphadenopathy in January 1968, but no penile lesions were present and a VDRL report was negative. Erythromycin was given orally for five days with prompt disappearance of all palpable lymph nodes.

The patient was then well until October 1968 when a slightly pruritic widespread papular skin eruption appeared, followed in about two weeks by generalized lymphadenopathy. The skin lesions were treated with cornstarch soaks. Biopsy of material from axillary and inguinal nodes in November was interpreted as giant follicle lymphoma, and the patient was subsequently referred to the Division of Radiation Therapy at Stanford University Medical Center for further evaluation and

treatment. He was taking no medications, had not used Dilantin® and had no history of mononucleosis, cat scratches, sweats, or fevers.

The patient, who was healthy-appearing, had generalized lymphadenopathy, including palpable epitrochlear nodes, all less than 2.5 cm in size. There was a generalized papulo-squamous eruption, most prominent on the palms and trunk. The remainder of the examination, including neurological, disclosed no abnormality.

The Venereal Disease Research Laboratory Test (VDRL) was reactive to 1:128 dilution and the Fluorescent Treponema Antibody Test (FTA) was also positive. The Stanford surgical pathologists were of the opinion that the lymph node biopsy sections showed reactive hyperplasia.

The patient was sent back to the referring physician with a diagnosis of secondary syphilis. A Jarisch-Herxheimer reaction developed during penicillin therapy, and palpable adenopathy disappeared within three weeks. A repeat VDRL was nonreactive within three months.

## Report of Second Case

*Case 2.* A 41-year-old single white man was well until January 1968 when he first noted small, painless, slowly enlarging masses on both sides of the neck. A generalized, erythematous and pruritic skin eruption was also noted. It cleared completely, without treatment, in a few days. There was no history of fevers, night sweats, diphenylhydantoin (Dilantin®) intake, cat scratches, mononucleosis, or penile lesions. A VDRL test had been negative in 1966, but the patient admitted to having both homosexual and heterosexual relations since that time.

After a March 1969 cervical lymph node biopsy was interpreted as showing Hodgkin's disease, the patient was transferred to the Palo Alto Veterans Administration Hospital for consideration of radiation therapy.

Except for generalized lymphadenopathy, including palpable epitrochlear nodes, no abnormality was noted on physical examination. All nodes were less than 2 cm in diameter. The liver and spleen were not palpable, and there were no skin lesions.

Results of blood cell count, urinalysis, determination of blood urea nitrogen, SGOT and electrolyte contents, and an x-ray film of the chest were all within normal limits. A VDRL test was reactive at 1:128 dilution and an FTA test was also positive.

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The reviewing pathologists interpreted the biopsy material as showing only lymphoid hyperplasia and not Hodgkin's disease. At that time, the VDRL results became available, and the clinical diagnosis of lymphadenopathy due to secondary syphilis was confirmed.

On March 30, 1969, 2.4 million units of Bicillin® were given, followed by a Jarisch-Herxheimer reaction within 24 hours. One month later, the patient was asymptomatic, no lymph nodes were palpable, and the VDRL was reactive only to 1:4 dilution.

## Discussion

These two cases illustrate the fact that syphilis is still a common although often overlooked disease which must be considered in the differential diagnosis of generalized lymphadenopathy. The VDRL remains an important routine screening test, particularly when epitrochlear nodes are palpable and a skin eruption involving the palms and soles is present, as in Case 1. If, as in both of these patients, the VDRL is positive, then the diagnosis of

syphilis can be confirmed by obtaining a positive FTA test. When skin lesions are present, particularly in the patient with a history of many sexual contacts who has generalized adenopathy, appropriate expert dermatologic consultation should be obtained and lesions or pathologic specimens examined for spirochetes.

That lymph node material from patients with secondary syphilis can be confused with lymphoma on biopsy is well shown by these two cases.

## Summary

Two case histories are described in which the generalized lymphadenopathy of secondary syphilis was present, lymph node biopsy was performed, and referral was made with the erroneous diagnosis of lymphoma in each case.

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## INTRACTABLE ASCITES

"Abdominal paracentesis . . . as an initial procedure in the management of intractable ascites does have distinct value. It has diagnostic value and will effect an immediate reduction in ascites and, perhaps more important in some of these patients, a reduction in portal hypertension. Given a patient with massive ascites and bleeding varices as he enters the emergency room, I do feel a very reasonable and helpful adjunct to therapy is to remove the ascitic fluid as soon as possible in order to reduce portal hypertension. The use of paracentesis as a chronic measure, I think, is contraindicated. It merely depletes the patient of already sorely needed protein sources and is relatively ineffective. It's associated with an incidence of infection and other complications. So as a chronic measure, paracentesis should not be considered in the therapeutic regimen."

—FENTON SCHAFFNER, M.D., New York City  
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## Graves' Disease in Non-Identical Twins

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THERE HAVE BEEN several reports of Graves' disease (diffuse toxic goiter) in identical twins.<sup>1-8</sup> The following report of its occurrence in a set of non-identical twins of opposite sex appears unique in the literature.

*Case 1:* Beginning in January 1969, the patient, a 22-year-old white man, had gradual onset of weight loss, excessive appetite, weakness, palpitation, sweating, diarrhea, and prominence of the eyes. In August 1969, his pulse rate was 100 per minute. There was a prominent stare, tremor, warm moist skin and brisk reflexes. The thyroid gland was diffusely enlarged, and a bruit could be heard. The  $I^{131}$  uptake was 49 percent (normal 15 to 45 percent), serum  $T_4$  11.8 micrograms per 100 ml (normal 3 to 6.5 micrograms) and the  $T_3$  resin uptake 43 percent (normal  $29 \pm 5$  percent). The patient improved with propylthiouracil therapy.

*Case 2:* The patient, a twin sister of the patient in Case 1, suffered anoxia and brain injury at birth and now spends nine months a year in an institution for retarded persons. In May 1969 she became extremely nervous and irritable and had a 20-pound loss in weight. The pulse rate was 140 per minute and the blood pressure 180/70 mm of

mercury. The thyroid gland was diffusely enlarged. Protein-bound iodine was 12.2 micrograms per 100 ml and the  $T_3$  uptake was 43 percent.\* She responded to propylthiouracil.

### Discussion

It has been recognized that hereditary predisposition to the development of Graves' disease exists and it is postulated that the gene is transmitted as a multifactorial genetic inheritance.<sup>9-15</sup> The familial incidence of Graves' disease has been as high as 60 percent in some series.<sup>9-11</sup> Martin and Fisher found a higher incidence among siblings than among parents in the families of 90 probands with Graves' disease—16 of 160 siblings as against 1 of 180 parents.<sup>10</sup> The simultaneous occurrence (concordance) of Graves' disease in both members of non-identical twins has been reported rarely. In an extensive survey of Danish twins,<sup>4</sup> 58 sets were found in which at least one member of the pair had Graves' disease (thyrotoxicosis and goiter). Twenty-one were identical twins and 37 were non-identical. The incidence of concordance among the identical twins was 76 percent (16 of 21). Only 10 percent of the non-identical twins were concordant for Graves' disease (4 of 37). It is interesting that the four non-identical twins concordant for the disease were of the same sex.

\*Performed at another institution. Normals unknown.

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# Recent Advances in Surgery of Congenital Heart Disease

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■ *In the cyanotic group palliative procedures for transposition of the great arteries are frequently life-saving in infancy, and the definitive operations such as the atrial baffle, and the Rastelli procedure for those with ventricular septal defect and pulmonic stenosis, are now firmly established. In tetralogy of Fallot shunting procedures continue to be employed in infancy and early childhood, and the complete repair is usually done after the age of five. Corrective operations for total anomalous venous return may have to be staged, and the results are more satisfactory in older children. The various forms of endocardial cushion defects can usually be recognized accurately preoperatively, and where the normal anatomical relationships can be restored, excellent results obtained. Brilliant operative success can now be had in some forms of truncus arteriosus and double outlet right ventricle.*

*It is quite common to find congenital heart disease in adults, frequently after many years of having been treated as rheumatic heart disease. The operative risk in this group is less than 10 percent, and in most instances such patients are restored to their normal physiological age after operation.*

REMARKABLE ADVANCES have been made in the surgical treatment of congenital cardiac malformations in the past decade. Many of the old procedures have established a permanent place in surgical therapy, while new operations are being

devised for hitherto uncorrectable complex lesions. If the 1940s are to be remembered for the beginning of surgical correction of extracardiac lesions (patent ductus arteriosus and coarctation) and the 1950s for the introduction of extracorporeal circulation, the past decade will be remembered for the improvement in mortality statistics as surgeons continue to learn more about preoperative, intraoperative, and postoperative care of the patient with congenital heart disease.

Healthy development in this field is noted in attempts to establish classification, nomenclature, criteria for diagnosis (New York Heart Association, 1964)<sup>1</sup> development of a method of coding

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TABLE 1.—*Procedures Used in Treatment of Transposition of the Great Arteries*

Palliative:	
1.	Creation of atrial septal defect (Blalock and Hanlon, 1949).
2.	Baffes' operation (1956).
3.	Balloon septostomy (Rashkind et al, 1966).
4.	Edwards' procedure (1966).
Corrective:	
1.	Correction at the atrial level (Senning, 1959 and Mustard, 1964).
2.	Correction at the arterial level (Kay, 1955).
3.	Correction at the ventricular level (Rastelli, et al, 1969).

TABLE 2.—*Results of Mustard Operation<sup>11</sup>*

Author	Type I Transposition with Intact Septum		Type II with VSD Transposition		Type III Transposition, VSD and Pulmonary Stenosis	
	Patients	Mortality (Percent)	Patients	Mortality (Percent)	Patients	Mortality (Percent)
Aberdeen	35	14	13	15	1	100
Cooley	9	28	5	80	8	75
Kirklin	6	16	13	30	2	50
Mustard	18	29	6	84	4	100

for data processing systems (Kerth et al)<sup>2</sup> and cooperative studies involving various centers (Kittle, 1968)<sup>3</sup> regarding "categorizing and defining quantitatively the preoperative observations which are predictive of risk and quality of survival."

The purpose of this communication is to review briefly the new developments in the surgical therapy of congenital heart disease and also to analyze the results of operation for common congenital cardiac defects from various centers including our own. The shortness of this review necessitates exclusion of many excellent series. Adequate description of the procedures or acknowledgement of the contributions from many distinguished contributors is impossible for the same reason.

## Cyanotic Group

### *Transposition of the Great Arteries*

Transposition of the great arteries is the commonest cause of mortality in infants born with congenital heart disease. Eighty-six percent of these children die during the first six months of life. As the operations for this anomaly have to be performed in very small infants, the surgical risk is extremely high. In recent years, a number of palliative and corrective procedures have been available since the creation of an atrial septal defect was suggested by Blalock and Hanlon.<sup>4</sup> (See Table 1.)

Among the palliative procedures, the Blalock-Hanlon operation has been the most commonly employed, even though the lowest mortality figure reported with this operation is 18 percent (Ochsner et al).<sup>5</sup> In the future, however, balloon septostomy, as described by Rashkind,<sup>6</sup> will be used more frequently because of the low mortality associated with it.

Until recently, the reports of successful total correction of transposition of the great arteries were few and isolated (Senning,<sup>7</sup> Kirklin<sup>8</sup>). In 1964, Mustard<sup>9</sup> described a method of correction at the atrial level, using a pericardial baffle on a principle described originally by Albert.<sup>10</sup> Subsequent use of this procedure by other surgeons was very prompt and their results are compared in Table 2.<sup>11</sup> For transposition with pulmonic stenosis and ventricular septal defect, the results of the Mustard operation are not so satisfactory. Rastelli et al, 1969<sup>12</sup> recently devised a new method of correction at the ventricular level and used it successfully in several children. The reader is referred to their excellent paper for the details of the correction, which basically consists in using a prosthetic baffle between the ventricular septal defect and the aortic orifice so as to divert the flow of blood from the left ventricle to aorta. An aortic homograft or autologous fascia lata graft is used to reconstruct a new right ventricular outflow tract from the anatomic right chamber.

### *Tetralogy of Fallot*

Surgical treatment for tetralogy of Fallot is 25 years old, a quarter century having passed since Blalock and Taussig devised a method of systemic-pulmonary anastomosis for this anomaly which comprises 30 percent of the cyanotic group and 11 percent of all congenital cardiac malformations. Table 3 lists a number of palliative and corrective procedures in use for tetralogy. The variation in the degree of outflow obstruction of the right ventricle in tetralogy accounts for such a variety of surgical procedures and the need for surgery at the different levels.

Early palliative shunting procedures are required for many of the severely cyanotic infants. In the infants who have anoxic difficulties before the age of two months, the outlook may be poor because of atretic pulmonary vessels; however, it is frequently possible to perform a systemic-pulmonary artery anastomosis even in small infants. It is usually technically more satisfactory to use

TABLE 3.—Surgical Procedures in Use for Tetralogy of Fallot

Palliative:	Corrective:
Systemic-Pulmonary shunts	• Lillehei (1955)
• Blalock-Taussig (1945)	
• Potts (1946)	
• Glenn (1956)	
• Waterston (1962)	
Direct attack on pulmonic valve	
• Brock (1948)	

TABLE 4.—Surgical Mortality of Blalock-Taussig Operation

Author	Number of Cases	Mortality (Percent)
Taussig-Bauersfeld (1953)	857	15.0
Möller (1962)	148	14.9
Hallman-Cooley (1963)	205	8.3
Gerbode (1963)	132	8.5
Shumacker-Mandelbaum (1960)	115	4.3
Sulamma (1964)	51	3.9

the subclavian artery arising from the innominate.<sup>13</sup> The results of this operation are summarized in Table 4. The Potts<sup>14</sup> type of anastomosis and the Glenn<sup>15</sup> procedure are not as frequently used because of the technical difficulty at the time of total correction. Some surgeons prefer the Waterston type of shunt, between the ascending aorta and right pulmonary artery.<sup>16</sup>

Most surgeons prefer not to operate for total correction in children less than five years of age, although others are ready to lower this age limit to three. The surgical mortality for total correction has improved considerably since Lillehei's<sup>17</sup> first attempt under cross circulation. This certainly can be attributed to better understanding of the anatomic features of the lesion and the conduction system of the heart, and to greatly improved methods of perfusion and postoperative care. (See Table 5.)

#### Anomalous Pulmonary Venous Drainage

This anomaly, which frequently is fatal during the first year of life, consists of all the pulmonary veins opening into the right atrium by means of a left superior vena cava or various other partial or total venous return to the right atrium, coronary sinus, or inferior vena cava. In total anomalous venous return, the systemic distribution of blood occurs through a patent foramen ovale. Often in this condition congestive failure develops in early infancy. The corrective operation for this abnormality consists of the anastomosis of the left

TABLE 5.—Surgical Mortality of Total Correction of Tetralogy of Fallot

Author	Number of Cases	Mortality (Percent)
Kirklin (1965)	509	7.0
Kimoto (1965)	72	19.0
Zenker (1964)	216	24.0
Zerbini (1965)	221	13.5
Gerbode (1963)	75	13.0
Kay (1959)	50	18.0
Barnard & Schrire (1961)	42	17.0
Mustard (1962)	188	13.0
Shumway (1965)	44	
Malm (1963)	41	

atrium to the common pulmonary vein which lies behind it, and ligation of the left superior vena cava. As some of the patients have a hypoplastic left heart, Mustard<sup>18</sup> suggested delaying closure of the atrial septal defect in these cases. Another method we have used is delayed ligation of the left superior vena cava. Pulmonary edema is the leading cause of death in such patients after surgical repair. The results of operation for partial anomalous venous return are excellent. The mortality rate for surgical operation in total anomalous venous return in infants is 53 percent,<sup>19</sup> whereas in the older age group the prognosis is much better. Occasionally, one finds adults who have escaped diagnosis of total anomalous venous return during childhood, but who can be operated upon successfully. One of these had served in the infantry in the last European war.

#### Rare Anomalies

Among the less common cyanotic conditions, new methods of corrections have been suggested for tricuspid and pulmonary atresia, and Ebstein's malformation of tricuspid valve. The superior vena cava to right pulmonary artery anastomosis<sup>15</sup> has provided good temporary palliation in these cases.

*Tricuspid atresia.* Patients with tricuspid atresia are cyanotic, have left ventricular hypertrophy, and a heart of relatively normal size because of the atretic tricuspid valve and hypoplastic right ventricle. Operation is usually required early in infancy because of the high mortality during the first year of life in untreated cases. Excellent palliation can be obtained by systemic-pulmonary artery shunt or the Glenn operation, but recently Rams et al (1966)<sup>20</sup> suggested an operation which seems quite imaginative. They described a three-stage correction for this condition: Glenn operation in the first stage, an anastomosis between right

atrial appendage and main pulmonary artery as the second stage and closure of the atrial septal defect in the third and final stage.

**Pulmonary atresia.** Pulmonary atresia with normal aortic root is another uncommon but challenging anomaly because of the mortality rate of 80 percent during the first year of life. In this condition the pulmonary valve and artery are hypoplastic and the right ventricle rudimentary. Life is maintained by a patent ductus arteriosus, closure of which accounts for the shortened life span. Shunting procedures are feasible but mortality is high. Campbell<sup>21</sup> collected reports of 27 cases and noted good results in only 25 percent. Four patients in his own purview went on to survive to the ages of three, five, eight, and ten years with shunt operations. Sometimes it is better to do both caval and systemic shunts in these patients.

**Ebstein's anomaly.** In this malformation there is abnormal displacement of tricuspid valve into the right ventricle. In correcting it, one has to take into consideration the conditions of valve leaflets and atrialized right ventricle distal to the valve. If the valve is fairly normal, it is possible to return the valve and its annulus to the annulus fibrosis with the excision of atrialized portion of right ventricle, as done by Hardy and his associates.<sup>22</sup> However, if the valve leaflets are severely deformed they have to be removed and a prosthetic valve inserted.<sup>23</sup>

## Acyanotic Group

### Septal Defects

**Ventricular septal defect.** Ventricular septal defects with pulmonary hypertension constitute a major challenge during infancy, whereas mortality for operating upon defects with normal pulmonary artery pressure is approaching zero. Most infants with ventricular septal defects can be managed by medical regimen during the first year of life, while some may require pulmonary artery banding because of high pulmonary flow. This procedure carries an acceptably low mortality and allows the surgeon a period of two to three years for definitive open heart repair.<sup>24</sup> In the presence of severe left ventricular failure, progressive pulmonary vascular disease and severe growth failure, an early intracardiac repair of the ventricular septal defect may be preferable to pulmonary artery banding. An ideal candidate for intracardiac repair, however, is a child more than five years old with large left-

TABLE 6.—*Surgical Mortality: Endocardial Cushion Defects—Partial A-V Canal*

Author	Number of Cases	Mortality (Percent)
Scott (1962)	32	19
Mustard (1965)	61	16
McGoan (1959)	35	6
Barnard (1968)	28	7
Gerbode (1967)	39	5

TABLE 7.—*Surgical Mortality: Endocardial Cushion Defects—Complete A-V Canal*

Author	Number of Cases	Mortality (Percent)
Mustard (1965)	23	73
McGoan (1959)	15	73
Scott (1962)	12	67
Barnard (1968)	6	33
Gerbode (1967)	29	30

to-right shunt with a slight to moderate elevation of right ventricular pressure. We believe that virtually all ventricular septal defects with shunts above 2 to 1 should be closed by the age of ten, since the chances of spontaneous closure beyond that age are minimal.

**Atrial septal defects.** Closure of an atrial septal defect of secundum type is one of the most gratifying operations in cardiac surgery. The mortality is less than 2 percent.<sup>25,26</sup> We recommend operation in all children five years of age or older who have shunts greater than 1.5 to 1.

**Endocardial cushion defects.** This term was introduced by Watkins and Gross.<sup>27</sup> It includes a group of defects previously called partial or complete atrioventricular canal. Our preference is, however, for the classification of Paul<sup>28</sup>: ostium primum defect, with cleft mitral valve, with cleft tricuspid and mitral valves, and atrioventricular communis with ventricular septal defect and mitral and tricuspid valves appearing as common valve. Our preferred method of repair of the different types is described elsewhere.<sup>29</sup> The mortality associated with operating upon patients with complete A-V canal is understandably high because of the anatomical complexities, and low in the partial A-V canal group. The high mortality in the former group (Tables 6 and 7) is mainly due to the lack of satisfactory cusp tissue (as a result of which neither the valves nor the defect can be repaired), surgical heart block, and frequent association of other anomalies. Patients who survive operation are generally greatly improved or, in fact, completely cured.



Stenotic Valve Lesions

Valvular pulmonic stenosis with intact ventricular septum represents about 10 percent of congenital abnormalities. In infancy, it constitutes a major threat to life if not recognized and treated early. Infants with one anoxic episode or in congestive failure require immediate operation, while older children with gradients across the pulmonary valve can be operated upon electively. The operative approach is either transventricular or transarterial via pulmonary artery. Although blind valvotomy and the open operation utilizing inflow occlusion and hypothermia have been employed, it is our preference to perform the open procedure with the aid of extracorporeal circulation in nearly all instances, as the operative risk is less and the result more satisfactory.

Congenital Aortic Stenosis

This condition may be valvular, subvalvular, supravalvular or a combination of these. Severe valvular stenosis can be the cause of sudden death in childhood, but the usual symptoms are fatigability, exertional dyspnea, angina pectoris and syncope. Though the valvular stenosis is the most common, muscular subaortic stenosis is the lesion which has been the subject of recent clinical curiosity and investigation.<sup>30</sup> The results of surgical treatment in muscular subaortic stenosis are very satisfactory. Although several methods of relieving the obstruction have been suggested we have found that very satisfactory results, with no mortality, have been obtained with a method similar to that described by Trimble<sup>31</sup> and Morrow.<sup>32</sup> For valvular stenosis, careful commissurotomy is necessary and residual gradients are common. For supravalvular stenosis a prosthetic gusset is used for widening the orifice. At present there is no acceptable operation for hypoplastic aortic annulus.

Miscellaneous Congenital Anomalies

Persistent Truncus Arteriosus

In recent years there have been brilliant reports of successful operations for correction of complex anomalies which were previously considered untreatable. Persistent truncus arteriosus is a condition in which a pulmonary artery arises from a single aortic vessel, the truncus, where it leaves the base of the heart. Also there is a high ventricular septal defect. This single trunk supplies the coronary and the systemic and pulmonary circulation.

TABLE 8.—Results of Operation in Infants with Congenital Heart Disease Under the Age of Two Years

Author	Number of Cases	Mortality (Percent)
Zerbini (1964)	71	41
Thorkelsen (1964)	200	33
Cooley (1964)*	500	27
Gerboe (1964)	147	25
Aberdeen (1968)*	835	32

\*Under one year of age.

TABLE 9.—Mortality During the First Year of Life—(From Various Autopsy Series)

Congenital Cardiac Lesion	Percentage Dying Under One Year of Age—(Percent)
Pulmonary atresia	100
Transposition of great vessels	85
Tricuspid atresia	83
Total anomalous pulmonary venous drainage	80
Pulmonary stenosis	70
Coarctation of aorta	75
Tetralogy of Fallot	45
Ventricular septal defect	42

TABLE 10.—Results of Operation in Adults Over 21 with Congenital Cardiac Lesions

	No. patients	Hospital Mortality
Open Heart Operations		
Atrial septal defect (secundum)	126	6 ( 4.7% )
Endocardial cushion defects	16	2 (12.4% )
Tetralogy of Fallot	28	6 (21% )
Ventricular septal defects	21	1 ( 5% )
Pulmonary Stenosis	18	0
Ruptured aneurysms of the sinus of Valsalva	9	1 (11% )
Left ventricular outflow tract obstruction other than valvular aortic stenosis	12	2 (16.6% )
Miscellaneous	10	4
Subtotal	240	22 ( 9.1% )
Closed Procedures		
Patent ductus arteriosus	29	0
Coarctation of the aorta	33	2 ( 6% )
Congenital heart block	1	0
Subtotal	63	2 ( 3.2% )
Total	303	24 ( 8% )

Fifty percent of the children born with this anomaly are dead within the first six months of life and survival up to early adult life is possible only if the pulmonary arteries are small. Pulmonary artery banding is used as temporary palliation but the results are not satisfactory. Recently Wallace et al (in 1968)<sup>33</sup> and Weldon (in 1968)<sup>34</sup> devised a method of successful total correction. This consists of the closure of the ventricular septal defect and the reconstruction of a new right ventricular outflow tract and main pulmonary artery, utilizing a homograft ascending aorta with its aortic valve.

TABLE 11.—*Surgical Classification of Congenital Heart Disease According to Operability*

<b>I. Operable or Surgically Correctable Lesions</b>	
<b>A. Acyanotic Group</b>	
<b>1. Lesions With Abnormal Pulmonary-Systemic Shunts</b>	
(a) Excellent results as surgery is low risk	(b) High risk associated with operation
Patent ductus arteriosus	Pulmonary atresia
Atrial septal defect	Tricuspid atresia
Ventricular septal defect	Persistent truncus arteriosus with hypoplastic pulmonary arteries
Aorto-pulmonary window	Ebstein's anomaly with ASD and right-to-left shunt
Pulmonic stenosis with ASD	
Pulmonic stenosis with VSD (acyanotic tetralogy)	<b>2. Lesions Resulting in Increased Pulmonary Blood Flow</b>
Coronary arteriovenous fistula	(a) Excellent results as operation is low risk
Ruptured aortic sinuses of Valsalva	Partial anomalous pulmonary venous return
Partial atrioventricular canal	Total anomalous pulmonary venous return with normal pulmonary vascular resistance
Ebstein's anomaly with ASD and left to right shunt	Transposition of great vessels with intact ventricular septum
Left ventricle-right atrial communications	Congenital pulmonary arteriovenous fistula
Aberrant pulmonary artery	(b) High risk associated with operation
(b) High risk associated with operation	Truncus arteriosus
Complete atrioventricular canal	Double outlet right ventricle
Large ventricular septal defect with pulmonary hypertension during infancy	Transposition of great arteries with VSD or pulmonic stenosis
Preductal coarctation of aorta	
<b>2. Lesions Without Abnormal Pulmonary-Systemic Shunts</b>	<b>II. Nonoperable or Surgically Uncorrectable Lesions</b>
(a) Excellent results as operation is low risk	Single ventricle
Coarctation of aorta	Hypoplastic left heart syndrome
Pulmonic stenosis (isolated)	Mitral atresia
Congenital aortic stenosis	Aortic atresia
Anomalies of the aortic arch	Atresia of aortic arch
Anomalies of the coronary arteries	Hypoplasia of the aorta
(b) High risk associated with operation	Complete atrioventricular canal with severe deficiency of valve tissue
Tricuspid stenosis and atresia without ASD	Tricuspid and pulmonary atresia with transposition of great arteries
Ebstein's malformation without ASD	Truncus arteriosus with severely hypoplastic pulmonary arteries
Congenital mitral stenosis	Taussig-Bing anomaly
Cor triatriatum	<b>III. Lesions In Which Operation Is Contraindicated</b>
Ectopia cordis	Endocardial fibroelastosis
Congenital diverticulum of the left ventricle	Primary pulmonary hypertension
<b>B. Cyanotic Group</b>	Eisenmenger's syndrome: any lesion or combination of lesions in which shunt is reversed due to pulmonary circulatory obstruction
<b>1. Lesions Resulting in Decreased Pulmonary Blood Flow</b>	Von Gierke's disease
(a) Excellent results as operation is low risk	Idiopathic hypertrophy of heart (Familial cardiomyopathy)
Pulmonic stenosis as with ASD with right-to-left shunt	<b>IV. Lesions In Which Operation Is Usually Not Necessary</b>
Tetralogy of Fallot	Dextrocardia
Pentalogy of Fallot	Dextro-rotations
Abnormalities of cava: IVC or SVC to left atrium	Corrected transpositions

### *Double Outlet Right Ventricle*

Double outlet right ventricle, a rare but interesting anomaly, was formerly considered inoperable. In essence it is a variety of incomplete transposition in which the anterior-posterior relation of the great arteries may be normal but the aorta originates from the right ventricle. The only outlet to the left ventricle is through the ventricular septal defect. The correction described by Redo et al in 1963<sup>35</sup> and Kirklin in 1964<sup>36</sup> consists in the use of a prosthetic or tissue baffle so as to provide a tunnel between the ventricular septal defect and the aortic orifice. Usually the ventricular septal defect needs enlarging. With operation

the outlook is quite encouraging, for the life expectancy is poor in infancy. (In all 13 cases in the autopsy series from Johns Hopkins the patients were under six months.)

### *Cardiac Surgery in Infants*

Although the surgical mortality in the first two years of life was very high in early days of cardiac surgery there has been steady improvement due not only to advancements in technique and post-operative care, but equally to the current accuracy in diagnosis. (See Table 8.) Today it is customary to perform cardiac catheterization and angiography at any hour on an emergency basis. It must be



emphasized also that the first year of life is extremely critical for these infants. Table 9 gives the percentage of cause of death of infants lost under the age of 12 months.

## Congenital Heart Disease in Adults

Until fairly recently surgical treatment for the lesions of congenital heart disease often was delayed in adults in the belief that the patient had rheumatic heart disease. Greater use of laboratory diagnostic aids and more widespread recognition of clinical signs has changed this. Table 10 shows our operative experience in patients with congenital heart disease over the age of 21 years.<sup>37</sup> From the surgical results, it would be fair to conclude that in the absence of categorical contraindications, an adult with congenital heart disease is a proper candidate for surgical correction. Most of those who have complete repair are restored to approximately their normal physiological age.

On reviewing the experience in the past 30 years, it is possible to propose a classification on a surgical basis. The only possible use for such a classification is to outline what has been done and what remains to be done for the surgeon in this field. (See Table 11.)

In conclusion, the results of surgical repair for congenital heart disease have improved significantly in the past decade and many new procedures have become established for the correction of complex congenital abnormalities of heart for which only palliative operation was formerly available. In general, outlook for the future in this field is quite hopeful and one can safely predict further improvement in the results of operation because of our better understanding of the physiologic and anatomic features involved, as well as improvements in extracorporeal circulation and postoperative care.

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# The Hyperlipoproteinemias

## A Simplified Classification and Approach to Therapy

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■ *It is now clear that the various hyperlipidemias represent a heterogeneous group of disorders, each having various clinical and laboratory characteristics, prognosis and treatment. The three disorders commonly associated with premature atherosclerotic vascular disease are Type II (hyperbetalipoproteinemia), Type III ("broad beta" or "floating beta" disease) and Type IV (hyperprebetalipoproteinemia or, endogenous hypertriglyceridemia).*

*The diagnosis of each of these three disorders can be suggested by the fasting serum cholesterol level and the appearance of the fasting serum after it has remained overnight in a refrigerator. Type II disease is characterized by a clear serum and a pronounced to moderate hypercholesterolemia. It is treated by reducing dietary cholesterol and saturated fats, increasing dietary polyunsaturated fats, and cholestyramine. Type IV disease is characterized by a turbid serum indicating hypertriglyceridemia and a normal or only slightly elevated serum cholesterol level. It is treated with weight reduction, a low carbohydrate diet and clofibrate. Type III disease is characterized by both a turbid serum and increased cholesterol levels. It is treated with weight reduction, a low cholesterol diet and clofibrate.*

*With the treatment of all disorders the lipid values should improve; however, with the treatment of Type III disorder both triglyceride and cholesterol levels return to normal, xanthoma resorb and there is an improvement in the peripheral blood flow, indicating that there has been amelioration of the atherosclerotic process.*

ALTHOUGH IT HAS been long recognized that the level of serum cholesterol is a good indicator of the risk of developing premature coronary vascular disease,<sup>1,2</sup> this determination alone does not provide the physician with enough information for the rational approach to the therapy of the patient with hyperlipidemia. Over the past decade, many investigators have contributed significantly to our understanding of this heterogeneous group of disorders.<sup>3,4,5,6</sup> The classification system of Fredrickson, Levy and Lees based on the mobility of the various lipoprotein fractions provides us with the simplest approach to the understanding, diagnosis and treatment of the hyperlipoproteinemias.<sup>3,4</sup>

It is not the purpose of this paper to provide a complete review of this complicated field. Rather, on the basis of what has been learned about the typing system from lipoprotein electrophoresis and ultracentrifugation techniques, we would like to present a simple office approach to the diagnosis (Table 1) and management (Table 2) of these problems for practicing physicians.

It has been suggested that two pieces of information will provide the physician with an initial approach to the classification of the type of lipoprotein abnormality with which an individual patient may be afflicted.<sup>4</sup> These are the serum cholesterol after a 14-hour fast and the appearance of this serum after it has remained in the refrigerator overnight.

#### *Types I and V*

The appearance of the serum after standing overnight in a refrigerator will be either clear, turbid or creamy. If there is a definite cream layer which has separated from a turbid layer below, this indicates the presence of chylomicrons. Following a 14-hour fast, the only patients with hyperchylomicronemia are those with Type I or Type V hyperlipoproteinemia. Both of these disorders are characterized by a decreased tolerance to dietary fat which is not cleared from the blood.

Type I disease is rare, appears during childhood, associated with recurrent attacks of abdominal pain, and is caused by a deficiency in one or

more lipoprotein lipase. It is not associated with premature vascular disease and is treated by severe dietary fat restrictions.

On the other hand, Type V disease is characterized by endogenous as well as exogenous hypertriglyceridemia and usually is secondary to other disorders, namely, pancreatitis, diabetic acidosis, alcoholism, nephrosis and hypothyroidism. The familial nature of the primary form of this disease is not clear since the Type IV disorder will often occur in these families as well.

Both Type V and Type I disease are associated with attacks of severe abdominal pain, which usually respond well to marked restriction of the dietary fat intake. Treatment of Type V disease further consists of weight reduction and controlling the primary disorder when one is present. The association of coronary artery disease with Type V hyperlipoproteinemia is unclear.

#### *Type II*

We would now like to turn to Types II, III and IV hyperlipoproteinemia with which the association of premature coronary artery disease is quite clear. A recent study of patients with angiographically proved coronary artery disease demonstrated that 80 percent under the age of 50 years had Type II or Type IV disease, with about half of the patients in each group.<sup>7</sup> Although Type III disease is much less common, it is important to recognize it, since it is associated with generalized vascular disease and is exquisitely sensitive to treatment.

The determination of the Type II hyperlipoproteinemia abnormality in an office practice is quite simple (Table 1). The basic defect in this disorder is hyperbetalipoproteinemia probably secondary to decreased betalipoprotein catabolism,<sup>8</sup> resulting in elevation of serum cholesterol above 280 mg per 100 ml, usually without an associated rise in serum triglycerides. Therefore, the overnight serum of these patients is clear. Although tendinous and tuberous xanthoma are sometimes seen, in most patients with Type II disease the diagnosis will be missed if one depends upon finding xanthoma. When primary Type II disease is suspected, it is important to rule out the secondary forms. Hyperbetalipoproteinemia can be produced by excess dietary intake of cholesterol rich foods, hypothyroidism, myeloma, macroglobulinemia, liver disease and nephrosis.

Once it is suspected that Type II hyperlipoproteinemia is primary, it is most important to screen

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TABLE 1.—  
Hyperlipoproteinemia—  
Diagnosis

	II	III	IV
Cholesterol* Serum	↑↑ Clear	↑↑ Turbid	NI (↑) Turbid
Triglycerides Electrophoresis	NI (↑) ↑ Beta	↑ Broad Beta	↑↑ ↑ Pre-Beta
Ultracentrifugation			
<1.006	No Beta	Beta (TG/C < 2:1)	Pre-Beta (TG/C > 2:1)
>1.006	↑ Beta	NI Beta	NI Beta
CHO Induction	0	+	+
Xanthoma	O (Tendinous)	Palmar	O (Eruptive)

\*Note: All determinations of serum cholesterol and triglyceride are performed on blood drawn after a 14-16-hour fast, and the serum examined after being chilled 24 hours. Types I and V are distinguished by the presence of a cream layer on top of the chilled fasting serum, indicating the presence of chylomicrons.

NI = normal, TG/C = triglyceride to cholesterol ratio, CHO = carbohydrate.

TABLE 2.—  
Hyperlipoproteinemia—  
Treatment

	II	III	IV
Weight Diet	Balanced Cholesterol < 300 mg ↑ u/s fat	Same as II	Low CHO ↑ u/s fat
Drugs	Cholestyramine (Questran, Cuemid) 16-32 gm/day	Clofibrate (Atromid-S) 2 gm/day	(± Clofibrate)
Family screening	Adults— children mandatory	Adults	Adults

u/s = unsaturated to saturated fat ratio, CHO = carbohydrate.

other family members since there is a high probability that relatives will be affected by this autosomal dominant disease. Indeed, the demonstration of a serum cholesterol greater than 90 mg per 100 ml or a beta-cholesterol greater than 45 mg per 100 ml in cord blood will make the diagnosis in a newborn. After one year of age, the determination in a child of serum cholesterol greater than 260 mg per 100 ml or beta-cholesterol greater than 220 mg per 100 ml provides the diagnosis. The demonstration of this disorder in children gives a more helpful prognosis since they are often easier to treat by dietary alterations than are adults. Treatment of adults is difficult since the hyperlipidemia often responds poorly to dietary alterations and drugs (Table 2). Weight reduction is usually ineffective in reducing the level of serum cholesterol. Generally, a diet low in cholesterol (less than 300 mg per day), low in saturated fat and high in unsaturated fat will produce a 20 to 25 percent reduction in the serum cholesterol. The American Heart Association diet is suitable for this, provided egg yolks are completely excluded.

The drug of choice for this disorder is cholestyramine in doses from 16 to 32 grams per day. It is poorly tolerated by many patients, who complain of symptoms of nausea and constipation. But

if it is tolerated, an additional reduction in serum cholesterol can always be expected from it. The drug will frequently lower serum cholesterol to the normal range. Less effective forms of therapy are beta-sitosterol, nicotinic acid and D-thyroxine. Nicotinic acid often causes flushing in clinically useful doses and D-thyroxine often causes an exacerbation of angina pectoris in susceptible patients secondary to its metabolic effects. Clofibrate has been reported to provide only a slight reduction in serum cholesterol, averaging about 9 percent.<sup>9</sup>

#### Type IV

Type IV hyperlipoproteinemia is probably a heterogeneous group of disorders about which there is no universal accord.<sup>3,5,6</sup> Quite simply, this disease can be thought of as resulting from excess triglyceride production by the liver from dietary carbohydrates or under utilization of triglycerides by peripheral tissue. It is recognized by the finding of a turbid serum, which indicates hypertriglyceridemia, and a relatively normal or only slightly elevated serum cholesterol (Table 1).

On lipoprotein electrophoresis patients with this disease characteristically will be found to have particles of pre-beta mobility. Pre-beta particles are a complex of triglyceride with alpha and beta-



lipoproteins. This disease, likewise, may be a secondary manifestation of diabetes mellitus, pancreatitis, alcoholism, nephrotic syndrome, hypothyroidism, progestational hormones, weight gain or emotional stress. Further, since serum triglycerides rise after an acute myocardial infarction concomitant with a fall in serum cholesterol, phenotyping is best deferred for two months until the serum lipids have stabilized.

Unlike Type II disease, when the Type IV disorder is familial, it will be clinically manifest in less than 5 percent of the *propositi* before 20 years of age. Familial screening for this disorder, therefore, is best limited to relatives beyond the second decade.

One of the difficulties in making the diagnosis of Type IV hyperlipoproteinemia is that the level of serum triglycerides fluctuates widely from day to day. It is, therefore, imperative before this diagnosis is definitely established to have demonstrated a persistent hypertriglyceridemia, above 180 mg per 100 ml, on more than one fasting blood specimen. Likewise, response to treatment can only be definitely ascertained by the demonstration of a sustained reduction in the serum triglycerides. Since patients will show a decided increase in the level of the serum triglycerides with weight gain or with feeding of an isocaloric high carbohydrate diet (7 grams of carbohydrate per kilogram of body weight), treatment of this disorder is quite clear and consists of sharp reduction in total calories to achieve ideal body weight and restriction of the dietary carbohydrate intake. Dietary carbohydrate should be replaced with polyunsaturated fats. For this purpose, a modified diet such as might be prescribed for a patient with adult onset diabetes is usually quite adequate. Indeed, the distinction between the Type IV patient with abnormal glucose tolerance and the patient who has mild diabetes with hyperlipidemia is pragmatically nonessential. Both types of patients should be treated similarly, with weight reduction and carbohydrate restriction. With this therapy there is usually a significant number of patients who respond with a return of the serum triglycerides to near normal levels. For patients resistant to dietary management, clofibrate may be quite useful in a dose of 2 grams per day. Although clofibrate does not seem to prevent the hypertriglyceridemia which occurs with high carbohydrate feeding,<sup>9</sup> it is still effective in patients who are unable to follow an appropriate diet.

### *Type III*

Type III hyperlipoproteinemia is a unique, uncommon, familial, recessive disorder which is characterized by the production of an abnormal betalipoprotein with an unusually high affinity for triglycerides. Because of the high triglyceride content, this betalipoprotein will float on ultracentrifugation. In the preparative ultracentrifuge, the betalipoprotein of the serum will normally gravitate to the bottom of the test tube as the low density lipoprotein fraction. The abnormal betalipoprotein formed in patients with Type III disease, however, floats to the top of the tube and imparts to the very low density lipoprotein fraction an unusually high concentration of cholesterol. This characteristic has caused this disorder to be occasionally referred to as "floating beta disease." On lipoprotein electrophoresis the abnormal betalipoprotein displays a broad band of migration tending to overlap both the normal beta and pre-beta bands and has caused this disease also to be referred to as "broad beta disease."

This disorder cannot be diagnosed with certainty in an office practice, since ultracentrifugation techniques are necessary. However, the finding of an elevated serum cholesterol of 400 to 600 mg per 100 ml and a turbid serum suggests that it may be present (Table 1). An elevated serum triglyceride of roughly equal magnitude to the serum cholesterol increases the suspicion that the patient has this disorder. Clinically, one can be more certain of the diagnosis by the finding of palmar xanthoma which appear as yellow streaks in the palmar creases. This is highly characteristic of this disorder. One often sees tuberoeruptive xanthoma on the extensor surfaces of the extremities as well.

Although Type III hyperlipoproteinemia is uncommon, it is extremely important that patients so affected be recognized since treatment invariably produces dramatic results. Weight reduction and a low cholesterol, balanced diet can be actively combined with clofibrate therapy to reduce the serum cholesterol and triglyceride values to normal. Moreover, the sustained reductions in plasma lipid values often result in resorption of xanthoma and improvement in symptoms of intermittent claudication and angina pectoris.<sup>10</sup>

Although Type III disease is an uncommon disorder, it has provided a useful model to answer an important question which arose soon after the association between elevated serum cholesterol

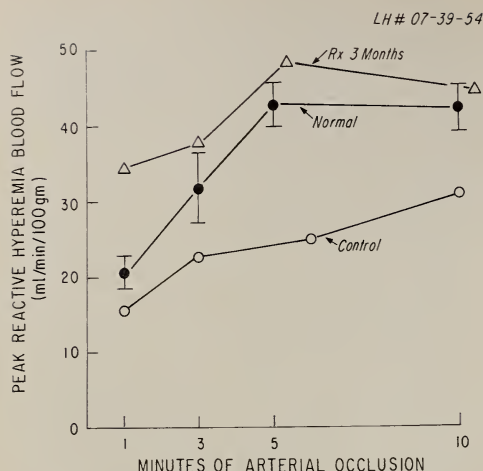


Chart 1.—Peak reactive hyperemia blood flow following release of various durations of arterial occlusion in 23 normal subjects (closed circles) ( $\pm$ SEM) and in a patient with Type III hyperlipoproteinemia before (open circles) and after (open triangles) three months of treatment with diet and clofibrate.

and coronary artery disease was recognized. That question was: Can one affect the course of vascular disease by altering the levels of serum cholesterol? Although population studies have tended to answer this question in the affirmative,<sup>11,12</sup> the results of prospective studies have not been striking and there has been one study which did not show increased longevity with the treatment of hyperlipidemia.<sup>13</sup>

Population studies, of necessity, require that large numbers of subjects be examined for a long period. Controlling all the variables in such an investigation often proves difficult. It would seem that examining the changes which take place in an isolated vascular bed in a single individual during treatment of the hyperlipidemia would provide a more direct answer. Since serial evaluation of the coronary circulation is difficult and since it is difficult to predictably maintain the serum lipids of patients with the more common Type II and Type IV disorders within normal limits for prolonged periods, it was decided to look elsewhere for an answer to this problem.

Specifically, it was noted that patients with Type III hyperlipoproteinemia have peripheral as well as coronary vascular disease. Functional evaluation of the peripheral circulation, unlike that of the

coronary circulation, is fairly easily accomplished by means of venous occlusion plethysmography.<sup>14,15</sup> It has been previously noted that the peak reactive hyperemia blood flow seen after release of five to ten minutes of arterial occlusion is a good indicator of the degree to which the peripheral circulation is affected by vascular disease.<sup>15,17</sup>

As can be seen in Chart 1, when the duration of arterial occlusion is prolonged beyond five minutes, there is no further increase in the peak blood flow response on restoration of the circulation. This has been considered the maximal ability of the blood vessels to dilate. It will be noted in the one patient shown with Type III disease before treatment that there was a decided limitation of the dilator capacity of the peripheral blood vessels secondary to peripheral atherosclerosis. However, after three months of therapy with diet and clofibrate which maintained the serum lipids at a normal level, the peak reactive hyperemia blood flow response returned to normal levels. This response to treatment was typical of the six patients studied with Type III disease and peripheral vascular disease. The average increase in peak blood flow was 55 percent in their most severely affected extremity.

Recent anatomic evidence helps to confirm our suggestion that the cholesterol in the atheroma of Type III patients is particularly labile.<sup>18</sup> We would further suggest that in patients with the Type II and Type IV disorders, in which the cholesterol in the lipid-rich plaques appears to be much less labile and for which the treatment is less satisfactory, perhaps with prolonged therapy there may be at least retardation of the progression of the vascular disease as well.

## Conclusion

From these observations it can be seen that the examination of the fasting serum cholesterol alone is not sufficient to diagnose and treat the various disorders of lipoprotein metabolism. However, with the simple expedient of examining the fasting serum after it has been allowed to remain in the refrigerator overnight, one can discover patients with lipoprotein abnormalities who would be missed by serum cholesterol determination alone. Furthermore, this procedure provides an initial approach to the classification and rational management of the particular type of disorder with which the patient is affected. It is only with proper classification that these various disorders can be

properly treated. In addition, recent research has suggested that with the proper treatment of these atherogenic disorders there may be not only an arresting of the atherosclerotic process but a reversal of the process as well.

#### TRADE AND GENERIC NAMES OF DRUGS

*Questran®*, *Cuemid®* . . . . . cholestyramine  
*Atromid-S®* . . . . . clofibrate

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#### CORTICOSTEROID EFFECT ON THE EYE

"Our laboratory assays of corticosteroid effect on the eye are crude and poor and approximate; and yet our own work, and particularly the work of David Brown, would indicate that taking an ordinary drop of dexamethasone (trade named Decadron) and diluting it approximately 1,000 times gives you topically in an experimental graft rejection system about the same kind of corticosteroid effect that you expect in a man taking 35 mg of prednisone daily. So that the effective steroid concentration you get in the cornea from oral corticosteroids seems incredibly less, at least in the system we used, than we get from topical corticosteroids. Or put another way, we can get enormously effective concentrations of corticosteroids in the cornea from topical administration—something you can't get when you consider kidney transplants, heart transplants, and things of that sort."

—HERBERT E. KAUFMAN, M.D., Gainesville, Ga.  
 Extracted from *Audio-Digest Ophthalmology*, Vol. 6, No. 23, in the Audio-Digest Foundation's subscription series of tape-recorded programs.



## MEDICAL STAFF CONFERENCE

# Technique, Rationale, and Usefulness of Bedside Right Heart Catheterization In Critically Ill Cardiac Patients

*These discussions are selected from the weekly staff conferences in the Department of Medicine, University of California, San Francisco. Taken from transcriptions, they are prepared by Drs. Martin J. Cline and Hibbard E. Williams, Associate Professors of Medicine, under the direction of Dr. Lloyd H. Smith, Jr., Professor of Medicine and Chairman of the Department of Medicine.*

DR. CRAWFORD:\* This is the first Medical Center admission for this 61-year-old, white man, who was referred for evaluation of severe congestive heart failure following a myocardial infarction. The patient had been in good health until four years before admission, when hypertension was discovered on routine physical examination. He was treated with methyl dopa and hydrochlorothiazide (Aldoril®). Eighteen days before admission, the patient experienced severe anterior, crushing chest pain radiating to the left arm. The pain was partially relieved by application of an ointment. Because of persistence of the pain the patient's physician had him admitted to hospital next morning.

Physical examination demonstrated evidence of mild, congestive heart failure, and an apical systolic ejection murmur was heard on auscultation of the chest. Electrocardiogram revealed evidence of an anterior septal myocardial infarction. On the 14th hospital day severe dyspnea suddenly developed. At that time an increase in the intensity of the systolic ejection murmur was noted and signs of congestive failure worsened. An electrocardiogram showed persistent ST segment elevation. The congestive heart failure could not be

controlled with digoxin and diuretics and the patient was referred to the Medical Center.

On admission he was observed to be overweight, tachypneic, pale, diaphoretic. The pulse was 100 beats per minute; blood pressure, 100 mm of mercury systolic and 60 mm diastolic; respirations, 26 per minute; and temperature 38°C (100.4°F). The jugular venous pressure was elevated to the angle of the jaw at 45°, and the carotid pulsations were full. A flat percussion note was heard at the lung bases, with decreased breath sounds and rales above the flat percussion note area. Examination of the heart revealed a right ventricular heave, a systolic thrill at the left sternal border, a normal first heart sound, a wide but physiologically split second heart sound, and a left ventricular gallop. A 4/6 systolic ejection murmur was heard to be loudest at the left sternal border but could also be heard at the right sternal border and axilla. At the lower left sternal border the murmur seemed to increase with respiration. A three component friction rub was heard at the left sternal border. The liver edge was felt 8 cm below the right costal margin. The extremities were cool and pale, with good pulses and no edema.

The patient was treated vigorously with digoxin, diuretics, and fluid restriction until multiple uni-

\*Michael Crawford, M.D., Intern in Medicine.

focal, ventricular premature contractions developed. He was then transferred to the coronary care unit and digitalis was withheld. Several days later, results of bedside right heart catheterization, performed by means of a small, flow-directed catheter, were diagnostic of ventricular septal defect. This diagnosis was confirmed by preoperative angiography. The patient's condition was stabilized on a vigorous medical management until the 69th day following myocardial infarction. On this day left ventriculotomy was carried out, with excision of a large aneurysm of the anterior left ventricular wall and repair of a 3 cm ventricular septal defect. The postoperative course has been uncomplicated and the patient is feeling quite well.

DR. SMITH: \* Thank you very much, Dr. Crawford.

Dr. Gold, may we see the radiographic films?

DR. GOLD: † The initial chest radiograph taken at the time of hospital admission demonstrated prominent pulmonary veins, suggesting moderate congestive heart failure with cardiomegaly and bilateral pleural effusions. Several days later signs of congestive heart failure appeared to be increased almost to the point of pulmonary edema. On later radiographs very prominent pulmonary arterial vessels appeared which looked like shunt vessels related to the presence of the interventricular septal defect.

DR. SMITH: The patient is not actually here for personal presentation this morning, although I gather he is doing quite well. We have asked Dr. Melvin Scheinman and Dr. Joseph Abbott to discuss this patient and the diagnostic approach of bedside right heart catheterization.

*Discussion by Dr. Scheinman‡ and Dr. Abbott§:*

Rupture of the intraventricular septum is a rare and frequently fatal complication of acute myocardial infarction.<sup>1,2</sup> This complication is most likely to occur within the first two weeks when the area of infarction is softest. The diagnosis is suggested by the abrupt appearance of signs and symptoms of both left and right heart failure together with a loud holosystolic murmur in a patient with a recent myocardial infarction. The electro-

cardiogram usually shows evidence of a recent transmural myocardial infarction and may reveal intraventricular conduction delays. The chest roentgenogram is characterized by an enlarged cardiac silhouette and pulmonary vascular congestion. Approximately 25 percent of these patients die within the first 24 hours and over 81 percent succumb within eight weeks.<sup>2</sup> Postmortem examination shows extensive infarction of both the muscular septum and the free wall of the left ventricle.

The clinical presentation of postinfarction ventricular septal defect often resembles that of acute mitral insufficiency resulting from rupture of a papillary muscle.<sup>3</sup> Correct diagnosis is more than an academic exercise because successful repair of septal perforations is possible.<sup>4</sup> The case presented this morning aptly demonstrates the value of bedside right heart catheterization for both diagnosis and quantitation of an acquired left-to-right ventricular shunt. In addition, the technique is of great value in monitoring critically ill cardiac patients.

Commonly used methods of hemodynamic monitoring are designed to determine whether left ventricular filling pressure and systemic flow are adequate to meet tissue needs. Left ventricular filling pressure can best be determined by direct measurement of left ventricular end-diastolic pressure (LVEDP). This can be carried out at the bedside by percutaneous insertion of a stiff, relatively large-bore catheter into a peripheral artery with retrograde passage into the left ventricle.<sup>5,6,7</sup> A recent collaborative study<sup>8</sup> documented the incidence of various complications (arterial thrombosis, hemorrhage, arrhythmia, and ventricular perforation) in patients undergoing left heart study in a cardiac catheterization laboratory. One can reasonably predict a significantly higher incidence of complications and death in critically ill patients studied at the bedside. Measurement of central venous pressure (CVP) is a more popular method of assessing left ventricular filling pressure.<sup>9,10</sup> Our studies, together with those of Loeb and coworkers,<sup>7</sup> show that CVP may in fact be a misleading index of LVEDP, especially in patients with acute myocardial infarction treated with inotropic or vasopressor agents.

Therefore, we use an alternative method of assessing both left ventricular filling pressure and systemic flow — namely, bedside flow-directed catheterization of the pulmonary artery. One end

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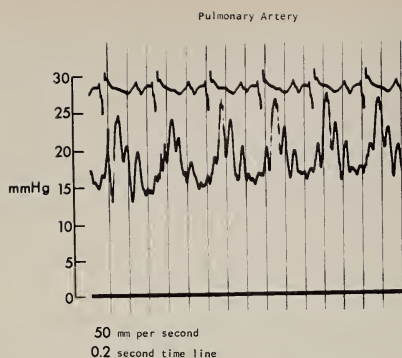


Chart 1.—A phasic tracing of the pulmonary arterial pressure wave recorded from the miniature catheter. The simultaneously registered electrocardiogram (upper tracing) allows correlation of electrical and mechanical events.

of a 100 cm-long nylon catheter\* (outside diameter, 0.37 inch; wall thickness, 0.07 inch) is flared to fit an adapter. The adapter is connected to a pressure transducer, and permanent records are obtained by recording simultaneously both the pressure waves and the electrocardiogram. The catheter, connected to the transducer, has a resonant frequency of 40 cycles per second with a damping coefficient of 0.40 at 98.6°F (37°C). Underdamped phasic pressure waves are recorded and are comparable in contour to those obtained from the larger and stiffer catheters used in the cardiac diagnostic laboratory (Chart 1). No premedication is required. The right or left antecubital fossa is scrubbed with hexachlorophene (pHiso-Hex®) and thimerosal (Merthiolate®) and draped appropriately. An 18-gauge, thin-walled needle is inserted into a medial antecubital vein, and the catheter is advanced through the needle into the vein. The catheter is flushed with a dilute heparin sodium solution and gently advanced into the pulmonary artery under electrocardiographic and pressure monitoring. Fluoroscopy is not employed. Abduction or external rotation of the limb usually overcomes any resistance to passage at the axilla. When the catheter is in the right atrium (judged by the length of catheter passed and the contour of the pressure record), introduction into the right ventricle and pulmonary artery is often facilitated by having the patient inspire deeply or rotate to either a right or left lateral decubitus position.

Pulmonary artery pressure is determined by the pulmonary blood flow, the resistance and compli-

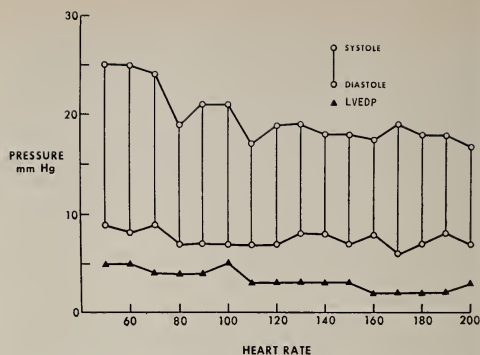


Chart 2.—The effect of change in heart rate on pulmonary artery diastolic and left ventricular end-diastolic pressures. The values represent averages of the control state in five canine experiments wherein heart rate was varied by atrial or ventricular pacing after sino-atrial heart block was induced. No increase in pulmonary artery diastolic pressure was produced by the tachycardia. Within the range of the heart rates studied, the pulmonary artery diastolic pressure accurately mirrored left ventricular end-diastolic pressure. (LVEDP=left ventricular end-diastolic pressure.)

ance of the pulmonary vascular bed, and the level of intra-alveolar, intrathoracic, and left atrial pressures.<sup>11</sup> In general, for any given left atrial pressure, changes in pulmonary artery systolic pressure reflect changes in stroke volume, while changes in diastolic pressure are indicative of changes in pulmonary vascular resistance.<sup>12</sup> Normally, the pulmonary capacitance is so great and its resistance so low that pulmonary artery diastolic pressure would be expected to be equal to or slightly greater than the pulmonary venous, left atrial or left ventricular pressures at diastasis.

Recently we studied the relationship between pulmonary artery and LVED pressures over a wide range of heart rates and left ventricular filling pressures in the open-chest, anesthetized dog. Catheters were inserted into the pulmonary artery, the left atrium, and the left ventricle while heart rate was controlled by sino-atrial node block and atrial or ventricular pacing. Using this preparation, heart rate was varied from 50 to 200 beats per minute. At the slowest heart rates, the difference between diastolic pulmonary and left ventricular pressures varied from 0 to 5 mm of mercury and graded increases in heart rate produced little change in the diastolic gradient (Chart 2). Similarly, when LVEDP was raised, either by increasing afterload (by mechanical aortic constriction or after administration of methoxamine hydrochloride) or pre-load (by rapid infusion of saline solution), both

\*Portex®, Smith Industries, Ltd., Jamaica, New York.



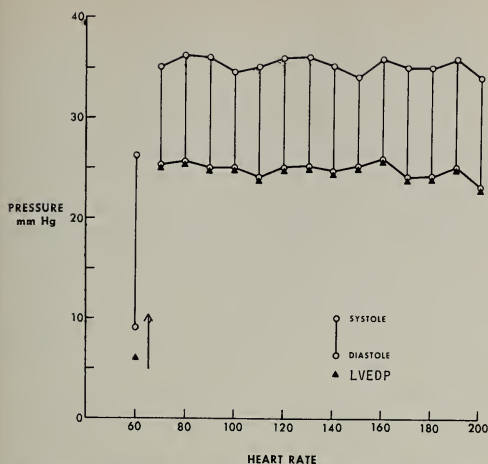


Chart 3.—The effect of change in heart rate on pulmonary artery diastolic and left ventricular end-diastolic pressures after increases in afterload or preload had induced an elevated left ventricular end-diastolic pressure (arrow). The values represent averages of five canine experiments wherein heart rate could be controlled by sinoatrial block and cardiac pacing. The gradient between the pulmonary artery diastolic and left ventricular end-diastolic pressures is abolished by elevation in left ventricular pressure. The identity between the diastolic pressures is maintained from the slowest to the fastest rate. (LVEDP = left ventricular end-diastolic pressure.)

diastolic pressures were identical over a wide range of heart rates (Chart 3). Thus, although the diastolic period was significantly shortened by acceleration of heart rate, the pulmonary artery diastolic pressure remained a sensitive indicator of LVEDP and this relationship was constant over a wide range of left ventricular filling pressures (0 to 25 mm of mercury).

Similar results have been reported in normal subjects studied over a wide range of heart rates and levels of cardiac output.<sup>13</sup> Kaltman and co-workers<sup>14</sup> showed a close correspondence between pulmonary artery and LVED pressures in patients with acquired heart disease: LVEDP varied from 6 to 18 mm of mercury and heart rate ranged from 60 to 140 beats per minute. Thus, pulmonary artery diastolic pressure appears to be a reasonable index of left ventricular filling pressures over a wide range of heart rates and ventricular end-diastolic pressures in both dog and man.

Certain limitations in the use of pulmonary artery diastolic pressure as a measure of LVEDP are apparent. First, patients with obstruction to pulmonary flow (either at the levels of pulmonary artery, capillary, or vein, or of left atrium or

mitral valve orifice) have a gradient of pressure at the end of diastole. Although pulmonary artery diastolic pressure is an invalid measure of the absolute level of LVEDP in these patients, changes in pulmonary artery diastolic pressure probably reflect changes in LVEDP. Patients with pulmonary hypertension secondary to chronic obstructive bronchopulmonary disease, for example, show parallel rises in pulmonary artery diastolic and pulmonary capillary wedge pressures following rapid intravenous infusions of dextran.<sup>15</sup> In addition, acidosis and hypoxia have important effects on pulmonary artery diastolic pressure independent of left ventricular filling pressure and therefore must be corrected before estimations of left ventricular competence are made on the basis of pulmonary artery diastolic pressure.<sup>12</sup> Finally, LVEDP can actually exceed pulmonary artery diastolic pressure in patients with congestive heart failure or with inflow obstruction secondary to severe left ventricular hypertrophy.<sup>16,17</sup> Augmentation of the atrial contraction results in a large "a" wave in the left ventricular pressure pulse with consequent elevation of the LVEDP. The "reversed" gradient is small in magnitude and probably of little clinical significance.

Our own experience has shown the pulmonary artery diastolic pressure to be a more sensitive index of LVEDP than CVP. For example, one-third of our patients with acute myocardial infarction complicated by pulmonary edema had a normal CVP at a time when pulmonary diastolic pressure was decidedly elevated.<sup>18</sup> A more significant finding was the poor correlation between changes in CVP and changes in pulmonary artery diastolic pressure.<sup>19</sup> Thus, the CVP often is an inaccurate reflection of left ventricular filling pressure.

We initially emphasized the desirability of monitoring systemic flow in critically ill patients. However, it is apparent that the critical factor in determining survival of patients in shock, for example, is not the level of systemic pressure *per se*, but rather the adequacy of the cardiac output to meet tissue needs. Goldman and coworkers<sup>20,21</sup> recently described the clinical usefulness of measurements of central venous oxygen saturation (CVO<sub>2</sub>) in monitoring patients with acute myocardial infarction. They found that patients with CVO<sub>2</sub> saturations of 60 percent or less tend to show evidence of either heart failure or shock or a combination of the two. This finding is not surprising since diminished cardiac output would be expected

to result in greater extraction of oxygen by peripheral tissues and therefore an abnormally low oxygen saturation in blood returning to the heart. Furthermore, it is apparent from the Fick equation

$$(\text{cardiac output} = \frac{\text{oxygen consumption}}{\text{arterial-mixed venous oxygen content}})$$

that cardiac output varies directly with mixed venous oxygen content when the oxygen consumption and arterial oxygen content remain constant. Although the  $\text{CVO}_2$  tends to be slightly lower than the mixed venous oxygen saturation ( $\text{MVO}_2$ )<sup>22</sup> (because of the large contribution of highly-saturated renal venous effluent returning via the inferior vena cava<sup>23</sup>), the  $\text{CVO}_2$  is still a reasonably valid reflection of  $\text{MVO}_2$  in normal subjects or in seriously ill patients without evidence of heart failure or shock. However, in patients in cardiogenic shock we found a reversal of the normal relationship in that  $\text{CVO}_2$  was consistently higher than  $\text{MVO}_2$ .<sup>24</sup> These findings are compatible with the thesis that low output states are attended by redistribution of blood flow away from the splanchnic, renal, and mesenteric beds toward the cerebral circulation, accounting for the disparity between  $\text{CVO}_2$  and  $\text{MVO}_2$ . These results do not negate the usefulness of serial  $\text{CVO}_2$  measurements in patients with severe low output states, since changes in  $\text{CVO}_2$  are far more important than the absolute levels and correlate well with corresponding changes in  $\text{MVO}_2$  in these patients.<sup>24</sup>

In addition to measuring right heart pressures and  $\text{MVO}_2$ , the flow-directed catheter technique allows for measurement of cardiac output by the Fick method when arterial blood and expired air are collected. Blood samples can also be obtained from chambers in the right side of the heart to establish or eliminate the presence of a significant left-to-right shunt. In addition, catheterization of the pulmonary artery allows quantitation of right-to-left shunts.<sup>25</sup> Depending on the clinical indications, the catheter may be left in place for hours or days. In this instance, the introducing needle is withdrawn from the vein and the catheter is taped directly to the skin and kept patent by a continuous dilute heparin drip.

In the past two and a half years we have attempted catheterization of the right heart at the bedside in 114 patients and succeeded in entering the pulmonary artery in 96 patients and only the right ventricle in 18 patients. The time necessary for completion of the procedure varied, but most

studies were performed within 30 minutes. There were no instances of lost or knotted catheters, phlebitis, emboli, infection, or death. Ventricular premature beats occurred commonly as the catheter entered the right ventricle, but in only three instances did a serious arrhythmia occur: Ventricular tachycardia developed in two patients and transient atrial fibrillation in the third patient. Ventricular tachycardia stopped spontaneously on removal of the catheter in one patient, although the other patient required a single 200 joule direct current countershock to the chest. These instances were unusual, however, for the catheter was well tolerated by most patients and has been left in the pulmonary artery for as long as six days.

The procedure is safe, provided certain precautions are followed:

- Catheterization should not be performed during the early phases of acute myocardial infarction, especially if the patient shows pronounced ventricular irritability. The two catheter-induced ventricular arrhythmias occurred in patients with acute myocardial infarction and premature ventricular beats who were studied within 12 hours of hospital admission.

- Patients with ventricular irritability should be treated with the appropriate antiarrhythmic agents before catheterization. The procedure should then be performed in an intensive care area with access to lidocaine and a direct current defibrillator. Since the establishment of these precautions, no serious arrhythmia has occurred in the patients studied.

In summary: The procedure is safe and easily mastered; in fact, most studies were performed by house officers under the supervision of the authors. Use of the pulmonary artery diastolic pressure as a measure of left ventricular filling pressure is valid in principle. In addition, the technique allows for serial measurements of  $\text{MVO}_2$  saturation or cardiac output and is thus extremely valuable in assessing hemodynamic dysfunction and the response to various therapeutic interventions in critically ill patients.

DR. SMITH: Before discussing these interesting suggestions and this technique, we should call on Dr. Benson Roe to comment more specifically about this patient and the findings at operation.

DR. ROE:\* I would like to stress the immense value derived from the routine use of the left

\*Benson B. Roe, M.D., Professor of Surgery.



atrial catheter in postoperative management of the valve replacement patient with low output syndrome. The inability to monitor the left side of the heart is a serious handicap in the management of left-sided functional abnormalities. We feel that the surgical opportunities in the treatment of patients with these severe consequences of acute myocardial infarction have not really been adequately utilized. All patients who are in shock or with very low cardiac output as a result of myocardial infarction should be monitored by this modality, their hemodynamic abnormality carefully assessed, and the opportunity for surgical intervention properly planned.

We felt it desirable to manage this patient conservatively so long as possible in the hope that the surgical techniques could be facilitated by the availability of scar tissue rather than dead myocardium. At a surgical meeting last week, the group from the Chicago Presbyterian Hospital reported six patients operated on following acute decompensation after myocardial infarction with five survivors. Three of these patients were operated on within two and a half weeks of their initial infarction and all survived. I feel that today's patient demonstrates an opportunity which is perhaps being neglected frequently in patients with severe myocardial infarction.

DR. SOKOLOV:\* I would like to reemphasize the importance of doing bedside cardiac catheterization in a patient of this sort, particularly in view of the difficulty in delineating a ruptured ventricular septum from mitral insufficiency secondary to malfunction of the papillary muscle. The murmurs are identical and cardiac failure may develop in both situations. Differentiation is important because mitral insufficiency can be corrected early in the course of the disease, whereas a ventricular septal defect requires ideally a period of one to three months before the repair can be made. In this patient the important factor in making the diagnosis was the oxygen content of the right ventricle. When failure develops in patients with myocardial infarction, one should employ these newer techniques in order to establish the diagnosis

so that surgical treatment can be instituted. I think everyone considered the possibility of ruptured ventricular septum in this patient, but differentiation from mitral insufficiency could not be made until the catheter data became available.

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# Interdepartmental Conference

FROM THE UNIVERSITY OF CALIFORNIA, LOS ANGELES, SCHOOL OF MEDICINE

## Diagnosis of Obstructive Jaundice

MODERATOR: JAMES S. CLARKE, M.D.

DISCUSSANTS: PETER BARRETT, M.D., ERIC W. FONKALSRUD, M.D., JOHN N. JOHNSON, M.D.,  
WILLIAM P. LONGMIRE, JR., M.D., MARTIN A. POPS, M.D., JOSEPH RÖSCH, M.D.,  
RICHARD J. STECKEL, M.D., AND MILO M. WEBBER, M.D.

*This is the edited transcription of an Interdepartmental Clinical Case Conference arranged by the Department of Surgery, University of California, Los Angeles, School of Medicine.*

■ The diagnosis of obstructive jaundice remains difficult yet vital, since operative decompression may relieve extrahepatic blockage, but operation can only harm patients with intrahepatic block or parenchymal cell inflammation or necrosis. Three new diagnostic methods (liver scanning, angiography, and transjugular transhepatic cholangiography) are reviewed, as is bilirubin metabolism, so important in the diagnosis of jaundice. Three clinical problems are discussed: extrahepatic obstruction due to cancer of the pancreas, biliary atresia causing jaundice in the newborn, and the diffuse ductal obstruction known as sclerosing cholangitis.

An accurate diagnosis can usually be made with standard diagnostic techniques, such as history, physical examination and biochemical tests, and, when appropriate, gastrointestinal x-ray studies, cholecystography and cholangiography, liver biopsy, observation of the patient's course, and the three new radiological approaches mentioned above. Extrahepatic obstructive jaundice is an indication for surgical treatment, except perhaps in cases of sclerosing cholangitis.

DR. JOHN N. JOHNSON (Department of Medicine): The patient was a 24-year-old Caucasian male welder who was admitted to UCLA on October 11, 1966 with chief complaint of easy fatigability, weight loss, and some abdominal pain approximately two and a half months before admission. He had been well until that time. These symptoms were progressive, and approximately two and a half weeks before admission were accompanied by nausea, vomiting and the passing of light-colored stools. About a week before admission the patient's complexion became yellow and he noticed a lightening in the color of his stools and a deep yellow color in his urine.

His past history was relatively uncomplicated. On physical examination the positive findings included pronounced scleral icterus. The heart and lungs were within normal limits; the abdomen was soft; the liver was palpable approximately 3.5 cm from the right costal margin and was very tender. No other masses or organomegaly were noted. Bowel sounds were normoactive. A stool was noted to be light-clay colored. There was no ascites. With the exception of the jaundice, the remainder of physical examination was within normal limits.

Leukocytes numbered 12,000 per cu mm, the hematocrit was 45, and hemoglobin was 15.4 grams per ml. Other pertinent laboratory data included an alkaline phosphatase value of 21, bilirubin of 7.4, SGOT of 240, SGPT of 272. Prothrombin time was 85 percent, heterophile 1:7, negative ANA. An upper gastrointestinal x-ray series suggested effacement of the second portion of the duodenum.

The initial diagnosis was infectious hepatitis. After an appropriate period of hospitalization, it became evident that the response was not of infectious hepatitis, but more suggestive of an obstructive type of jaundice.

On November 22, a transjugular cholangiogram showed a dilated common bile duct. Because of this finding, an exploratory laparotomy was performed, and a hard tumor mass was found at the head of the pancreas. The liver was noted to be studded with metastatic lesions. Pathology report verified adenocarcinoma of the pancreas.

Cholecystojejunostomy and jejunojejunostomy were performed, and the patient's postoperative course was uncomplicated. However, his enzymes

continued to increase and bilirubin to rise. He was discharged in December of that year to a nursing home.

DR. JAMES S. CLARKE (Department of Surgery): Moynihan said in 1926 that "no one living is infallible in the differential diagnosis of obstructive jaundice."<sup>8</sup> Today, this statement stands as a question—is it still true, or only an interesting historical relic?

By way of giving some perspective to the presentations which follow I wish to comment briefly on the selectivity exercised in developing the program of this conference. Of the many ways of approaching the diagnosis of a patient with jaundice, we have chosen only a few of the newer ones for discussion. While other methods, such as the history and physical examination, are still the cornerstone of accurate diagnosis, they cannot be reviewed in detail here. A history compatible with gallstones, cancer of the pancreas, a recent operation on the biliary tract, alcoholism, recent blood transfusions, or ingestion of drugs known to cause cholestatic jaundice would be of great help in the differential diagnosis of jaundice. Physical examination is likewise of primary importance, especially regarding the size of the liver and spleen, the palpability of the gallbladder, and the stigmata of cirrhosis of the liver. These aid in diagnosing and in the choice of proper tests for greater accuracy in the diagnosis.

Biochemical tests depend on the many synthetic and excretory functions of the liver and on the release of enzymes that occurs during cell destruction. Dr. Barrett will discuss those related to bilirubin metabolism. Unfortunately, biochemical tests are often confusing because of the mixture of bile duct obstruction and damage to the liver cells that is frequently the case in the jaundiced patient.

A liver biopsy specimen may be obtained at operation under direct vision, or by the transcutaneous route or a transjugular transhepatic route. The value and risks of obtaining specimens will not be discussed today.

Radiological examination includes the well-established upper gastrointestinal series and oral or intravenous cholecystography and cholangiography. Because of current great interest in the new radiological methods, our presentations will cover liver scanning, angiography, and transjugular transhepatic cholangiography.

Reprint requests to: Department of Surgery, UCLA School of Medicine, Center for the Health Sciences, Los Angeles, Ca. 90024 (Dr. Clarke).

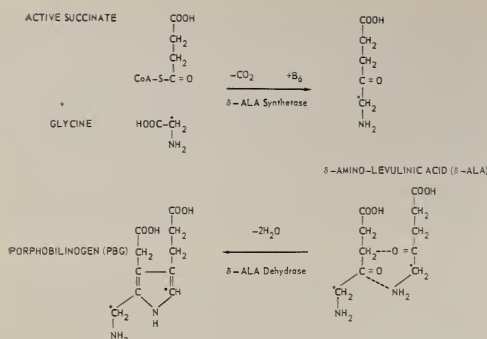


Chart 1.—The major steps in monopyrrole biosynthesis. The dots indicate the positions of the isotopic carbon atoms when glycine-2-C<sup>14</sup> is used as a precursor.

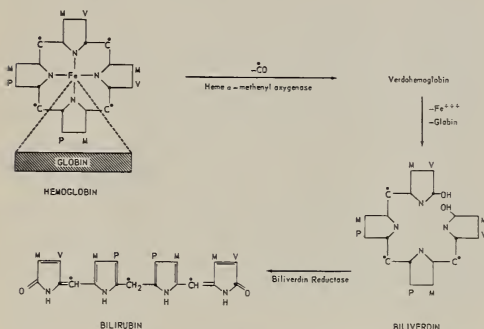


Chart 2.—The major steps in hemoglobin metabolism. Isotopic carbon atoms indicated by dots.

In addition to the case of cancer-derived obstructive jaundice presented by Dr. Johnson, we shall discuss two difficult problems in the field of obstructive jaundice: biliary atresia and sclerosing cholangitis.

## Bilirubin Metabolism In Obstructive Jaundice

DR. PETER BARRETT (Division of Gastroenterology): The presence of jaundice has attracted man's interest for centuries, an interest reflected by the fact that two of the four humours of classical Greek medicine were bile, yellow and black. Today our approach is a little more sophisticated, but many questions remain and one of the most interesting concerns the disposition of bilirubin in obstructive jaundice. It is well known that, in the presence of complete obstruction (which the patient presented probably had) the serum bilirubin

seldom exceeds 20 mg per 100 ml, yet it continues to be produced at a normal or even increased rate. I will return to this aspect of bilirubin metabolism presently.

In order to discuss bilirubin metabolism in the presence of extrahepatic obstruction, it is first necessary to review very briefly some aspects of normal bilirubin metabolism.

Charts 1 and 2 summarize the steps involved in the production of bilirubin. Hemoglobin is the best known hemoprotein, but the heme moiety is a critical portion of a variety of different enzymes, myoglobin, and the cytochromes. When these compounds are degraded, the iron is plucked from the cyclic molecule, and scission of the ring occurs at the alpha bridge carbon position, resulting in the release of carbon monoxide. It is worth emphasizing that one mole of carbon monoxide is produced for each mole of heme which is degraded, and the measurement of the rate of carbon monoxide production has proved to be a useful index of heme turnover.

Bilirubin is the major degradation product of heme in the body, and this pigment is rapidly cleared from the serum by the liver. For example, if a tracer dose of C<sup>14</sup>-bilirubin is given to a normal person, less than 10 percent remains in the serum at the end of four hours.<sup>1</sup> Once the bilirubin enters the hepatocyte, it is probably bound to a specific protein during its journey to the endoplasmic reticulum, where conjugation of the molecule occurs.<sup>4</sup> Conjugated bilirubin is subsequently excreted into the bile canaliculus and then into the intestine.

The sequence of pathologic changes which occur in extrahepatic obstructive jaundice has been well described. In a typical case, the initial changes consist of cholestasis, infiltration of polymorphonuclear neutrophils and edema in the portal triads. With prolonged obstruction, the portal areas become enlarged with proliferating bile ducts, fibrous tissue, inflammatory cells, and histiocytes. Bile infarcts are pathognomonic of this condition, but are relatively uncommon and therefore of little assistance in the differential diagnosis of jaundice.

Using cytochemical techniques, an increased amount of alkaline phosphatase has been demonstrated in the bile canaliculi shortly after the onset of experimental obstruction, and the serum content of this enzyme begins to rise. It is of note that ligation of only one major hepatic bile duct will produce a rise in the serum alkaline phosphatase.



By contrast, in the presence of an otherwise normal liver, the same procedure will not lead to an elevation of the serum bilirubin, for there is adequate clearance by the non-obstructed liver. This concept is essential for an understanding of the disparity between the serum alkaline phosphatase and bilirubin which may be observed in the presence of focal metastatic disease or in the occasional case of blockage of the right or left hepatic duct by tumor or stone.<sup>11</sup>

The serum alkaline phosphatase determination is very useful in the differential diagnosis of jaundice, but there is a moderate amount of overlap between parenchymal and obstructive disease states. Consequently, one cannot be dogmatic about the presence or absence of obstruction on the basis of this test alone.

In the presence of common bile duct obstruction the intraductal pressure rises, and above a level of 23 mm of mercury the production of bile ceases and the serum bilirubin concentration begins to rise. The precise pathway by which bilirubin returns to the serum is still unsettled. It has been suggested that conjugated bilirubin might make its way from the bile canaliculus to the lymphatic system. However, experiments in dogs have shown that, although there is a sharp rise in the thoracic duct bilirubin concentration immediately following the ligation of the common bile duct, this elevation persists for only a few hours and then returns almost to normal despite persistent obstruction.<sup>3</sup> This suggests that lymphatic outflow is not a significant pathway for the return of bilirubin from the liver to the serum. Two possibilities remain: The conjugated bilirubin may return to the serum directly from the hepatocyte or, alternatively, it may be excreted into the bile canaliculus and then travel between the cells back to the sinusoid. This issue must still be considered controversial.<sup>14</sup>

Attempts have been made to differentiate parenchymal from obstructive jaundice on the basis of the ratio of direct to indirect bilirubin (that is, conjugated to unconjugated bilirubin); however, the two fractions are generally found to rise together in both types of jaundice and the ratio offers no assistance in the differential diagnosis.<sup>21</sup> The only situations in which this ratio is useful occur in patients with jaundice due to increased bilirubin production, as in hemolytic anemia, or in patients with metabolic defects such as Gilbert's syndrome, in which an elevation of the unconjugated fraction of bilirubin predominates.

Bilirubinuria occurs in patients with obstructive jaundice. The excreted pigment is the conjugated, water-soluble fraction and is thought to be excreted chiefly by a process of glomerular filtration.<sup>19</sup> However, as the amount which can be measured in the urine in the presence of extrahepatic obstruction usually represents less than 20 percent of the daily bilirubin production, it is necessary to invoke other pathways and mechanisms for the disposal of the remaining 80 percent. This leaves us with a perplexing situation: In a patient with complete obstruction, the bilirubin cannot be delivered into the gut, and only a small fraction can be found in the urine.

Recent studies in mutant rats that cannot conjugate and excrete bilirubin normally have shown that, after the infusion of radioactive bilirubin, most of the radioactivity appears in the bile, but as unidentified water-soluble compounds; very little material can be identified as bilirubin itself.<sup>15</sup> This demonstrates that alternate pathways of bilirubin degradation are present, at least in this species, and it is possible that similar mechanisms account for the disposition of bilirubin in the presence of obstructive jaundice in man.

It has been proposed that alternate pathways for bilirubin degradation occur in the endoplasmic reticulum, the site of many drug detoxification reactions. In this regard it is of note that in jaundiced patients the administration of glucocorticoids (compounds known to induce certain drug metabolizing enzymes) usually results in a fall in the serum bilirubin concentration. The decrease in the serum bilirubin is most pronounced in patients with hepatitis, and this fact has been utilized as an aid in the differential diagnosis of parenchymal and obstructive jaundice. In practice, however, the reliability of this test is uncertain, and it is seldom used.

Further research will provide a better understanding of the pathophysiology of obstructive jaundice and will allow improvement in the care of patients with this problem.

### Angiography in Differential Diagnosis

DRS. JOSEPH RÖSCH\* and RICHARD J. STECKEL (Department of Radiology): Angiography is a valuable technique in the differential diagnosis of obstructive jaundice.<sup>2</sup> It gives detailed information about pathologic processes involving the liver and

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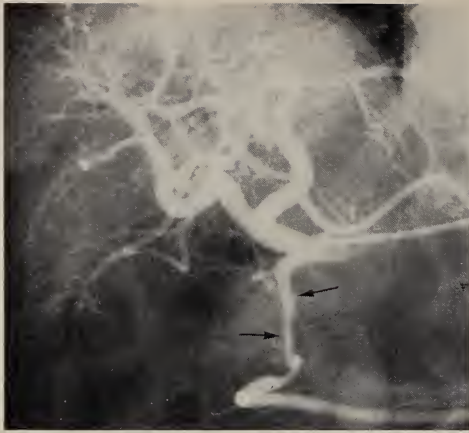


Figure 1.—Obstructive jaundice caused by pancreatic carcinoma. Hepatic arteriography; tumor infiltration of the gastroduodenal artery (arrows) and small pancreatic branches.

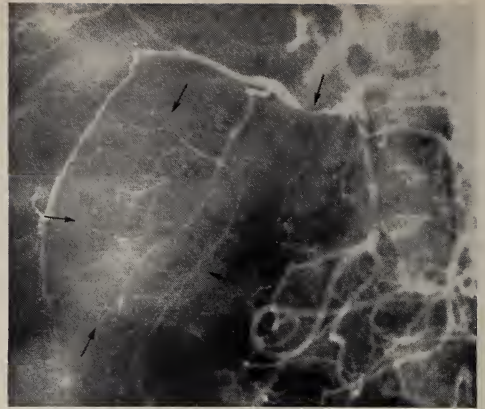


Figure 2.—Obstructive jaundice caused by carcinoma of the gallbladder spreading into the hepatic hilus. Superior mesenteric arteriography; arrows indicate tumor neovascularity occupying the entire gallbladder region and tumor infiltration of an aberrant hepatic artery.

individual organs in the subhepatic area, and often results in direct visualization of the lesion causing biliary obstruction. It is useful in demonstrating tumors of the pancreas,<sup>7</sup> gallbladder, bile ducts and liver (both primary and metastatic), and serves to differentiate them from non-neoplastic lesions. By determining the extent of a tumor and the secondary involvement of surrounding organs and vessels, angiography also contributes greatly to evaluation of tumor operability.

Selective studies of the celiac artery complemented by selective superior mesenteric studies, are the basic examinations used.<sup>10</sup> These procedures result in visualization of all organs in the upper abdomen and give a good impression of the portal circulation in the venous phase of the angiogram. For better evaluation of individual organs and increased diagnostic accuracy, superselective arteriography should be performed in questionable cases. Direct hepatic artery injection gives a good survey of the liver and gallbladder. Direct (superselective) gastroduodenal, dorsal pancreatic or inferior pancreaticoduodenal contrast injections are most suitable for diagnosis of disease in the pancreas or the duodenal papilla.<sup>12</sup>

Obstructive jaundice, whatever its cause, exhibits certain typical angiographic changes in the liver as a result of the cholestasis: because of the enlarged intrahepatic bile ducts, the hepatic vascular branches are narrowed and stretched, and the opacity of the liver in the capillary phase is irregular, with ribbon-shaped negative defects.<sup>13</sup> These

liver changes, combined occasionally with faint visualization of an enlarged gallbladder, are usually the only pathologic angiographic findings in cases without tumor. By contrast, biliary obstruction caused by tumors exhibit certain additional angiographic changes, which are of crucial importance.

*Pancreatic carcinoma* (Figure 1) is diagnosed principally by tumor infiltration of vessels. The smaller pancreatic arteries are affected first. They become irregular and narrowed with indented outlines, and may even appear amputated. Later on, an enlarging tumor will also infiltrate the adjacent major vascular trunks—the gastroduodenal, hepatic and superior mesenteric arteries, and the portal vein. Tumor neovascularity is usually not striking, consisting only of very fine vessels, and neovascularity usually is absent in the scirrhous type of carcinoma. The infiltrative changes in the vessels are of greatest importance in the differential diagnosis: in inflammatory enlargement of the pancreas, there is only displacement and mild deformity of the pancreatic branches or surrounding arterial trunks, but never signs of tumor invasion of the vessels.

*Cancer of the duodenal papilla*, particularly in its infiltrative form, also invades the nearby arteries. Only the small branches of the pancreaticoduodenal arcades are usually affected, appearing irregularly narrowed or amputated. Superselective injection techniques are essential for evaluating these small branches.





Figure 3.—Obstructive jaundice caused by carcinoma of the bile ducts in the liver hilus. Superior mesenteric arteriography; tumor infiltration of the aberrant hepatic artery and its main branches in the hilus (arrows).

*Cancer of the gallbladder* (Figure 2) exhibits tumor neovascularity as the main pathologic finding on angiography. The tumor vessels are irregular and sometimes straightened, and in other cases are tortuous and may form "vascular lakes." They are supplied primarily by the cystic artery and its branches. In cases with tumor infiltration into surrounding organs, the tumor vessels may acquire additional supply from the intrahepatic, duodenal or right colic arteries. A large tumor usually invades the adjacent vascular trunks, and the hepatic artery and the portal vein are most often affected.

*Cancer of the extrahepatic bile ducts* (Figure 3) is diagnosed by tumor infiltration of adjacent arteries, with the proper hepatic artery and its bifurcation usually affected. These arteries are irregularly narrowed and are often tortuous. With hepatic spread of the tumor, similar infiltrative changes are noted in the intrahepatic branches close to the liver hilus. There is also sometimes slight tumor neovascularity and tumor staining around the infiltrated vessels.

*Primary hepatoma* leading to obstructive jaundice (Figure 4) usually presents in a massive solitary form with perihilar localization. It is highly vascular and supplied by an enlarged hepatic artery. The tumor vessels are large and tortuous, forming bizarre vascular networks. Arteriovenous shunts may also be present, with filling of irregular vascular lakes. There is prominent "tumor staining," with the hepatoma becoming densely opacified in the capillary phase. Portal vein thrombosis

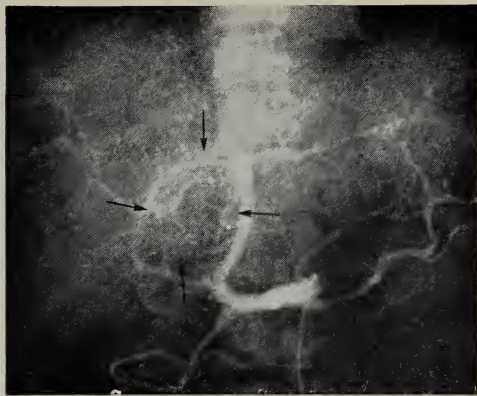


Figure 4.—Obstructive jaundice caused by primary hepatoma. Celiac arteriography; extensive tumor neovascularity in the hepatic hilus (arrows); infiltration of right hepatic branch, displacement of enlarged left hepatic branch.

is frequently visualized late in the angiogram, along with retrograde filling of a collateral venous circulation.

*Liver metastases* may have varying angiographic appearances, depending on their vascularity. Metastases from hypernephromas, thyroid or islet-cell carcinomas, hemangiosarcomas, and occasionally even colon carcinomas, may be highly vascular and may present with many irregular tumor vessels in the arterial phase, and with tumor "staining" of the metastatic deposits in the capillary phase of hepatic angiography. The angiographic diagnosis of poorly vascular or avascular metastases is based principally on deformity of the surrounding intrahepatic branches, and on filling defects in the liver parenchyma visible in the capillary phase.

In summary, angiography aids preoperatively in the differential diagnosis of obstructive jaundice of neoplastic origin. It demonstrates the tumor as well as its extent, and is of great assistance in evaluating potential operability.

## Liver and Pancreatic Scanning

DR. MILO M. WEBBER (Department of Radiology): As far as definition of the images is concerned, what I have to show here is going to be a poor second to the radiographic procedures. However, the entire principle is relatively new and, I think, measured against radiography and the advances we have seen in the past 60 or 70 years is equivalent to radiography back in the 1910s or



TABLE 1.—*Liver Scanning Agents*

<i>Agent</i>	<i>Tracer</i>
Radiogold .....	Au <sup>198</sup>
Rose bengal .....	I <sup>131</sup>
Human serum albumin (microaggregates) .....	I <sup>131</sup>
Human serum albumin (microaggregates) .....	Tc <sup>99m</sup>
Radiotechnetium-sulfur colloid .....	Tc <sup>99m</sup>
Indium colloid .....	In <sup>113</sup>

1920s. I think we have a long way to go, but the future is there.

Two procedures, liver scanning and pancreatic scanning, were of special importance in the case presented earlier. Before discussing them briefly, I would like to mention that liver scanning is in a broad sense a UCLA development, in that the first papers published on the subject were those of Dr. Stirrett and his associates back in the early 1950s.<sup>17</sup>

The technique of scanning is different from the technique of x-ray radiology in that the patient himself, rather than an x-ray tube, is emitting the photons. We attempt to make radioactive the part of the patient that we are interested in visualizing. In liver scanning we are limited to a few agents; Table 1 lists some of the most commonly used. Radiogold-198, in use throughout the world, is listed first. Rose bengal attracted originally a great deal of interest and is still used to some extent; in fact, it has a unique application (to be discussed later) in cases of obstructive jaundice.

The earliest liver scanning was done with serum albumin tagged with radioiodine-131, not in a particulate form at all, which collected to a minimal extent in areas of tumor activity.<sup>17</sup> The type of scan obtained in the early days was unsatisfactory in comparison with what we are capable of obtaining today. Small particles of serum albumin, prepared by heating and shaking, when given intravenously are concentrated by the reticuloendothelial system throughout the liver and spleen. When the scan is made, the liver and the spleen are visualized. The albumin particles can be tagged with radioiodine,<sup>18</sup> as they are in most places, or with radiotechnetium-99m, a relatively new tracer which permits the use of much more radioactivity with much less radiation damage.

Radiotechnetium-99m-sulfur colloid is a relatively new agent which consists of small particles of sulfur that include technetium sulfide; it is also localized within the reticuloendothelial system of the liver.<sup>9</sup> And, finally, Indium-113m, a new tracer which, like radiotechnetium-99m, has a very short half-life (approximately 90 minutes), can be used

in large doses and yields many photons yet delivers little destructive irradiation to the patient.<sup>5</sup> With these two agents the scan images appear to have fine detail, and we see things that we were unable to see with the older types of scanning techniques.

By the use of the techniques which involve uptake of tracer within the reticuloendothelial system we see the collection of cells that represent the active phagocytes of this system. Several patterns can be present in a normal person, and it is very difficult to say that one pattern is normal and another abnormal. In fact, there are probably 15 or so usual patterns; of those most commonly seen, we have selected four, shown in Figure 5, which represent what the liver scanning technique might be expected to show in a normal person.

Note that in some instances the left lobe is more prominent than in others; in Figure 5B it is almost separate—in fact, in some cases an actual cleft can be seen between the two lobes. The spleen shows up well at times, as in Figure 5C, where it is much more apparent than in 5A; the difference is due to the agent used (technetium-sulfur suspension in 5C, gold-198 in A). Another possible source of confusion is a Riedel's lobe extending from the tip of the right lobe.

In addition to the wide variation in the normal appearance of the liver, there is the problem of loss of detail due to the patient's breathing during the many minutes needed to perform a scan. There is also a limit to the size of the lesion that can be seen in the liver scan: it must be at least 2 to 3 cm in diameter (depending upon its location within the liver) for it to be discerned with certainty. If there are many small metastases scattered throughout the liver, we will be unable to see them. On the other hand, we can be sure to see large enough metastases, cysts or abscesses, even though we cannot really distinguish these processes from one another but see them all as areas of decreased tracer uptake. If they are too small, however, we may easily miss them.

Figure 6 is a good example of what might be seen in a patient with a tumor at the head of the pancreas, as in the case here presented. Note a light area, rather large, extending up from the hilar region of the liver, representing destruction of functioning reticuloendothelial cells throughout the liver in the region of the porta hepatis.

Figure 7 also shows the possible result of a tumor in the pancreas. The left lobe cannot be seen; its absence could represent that a tumor has

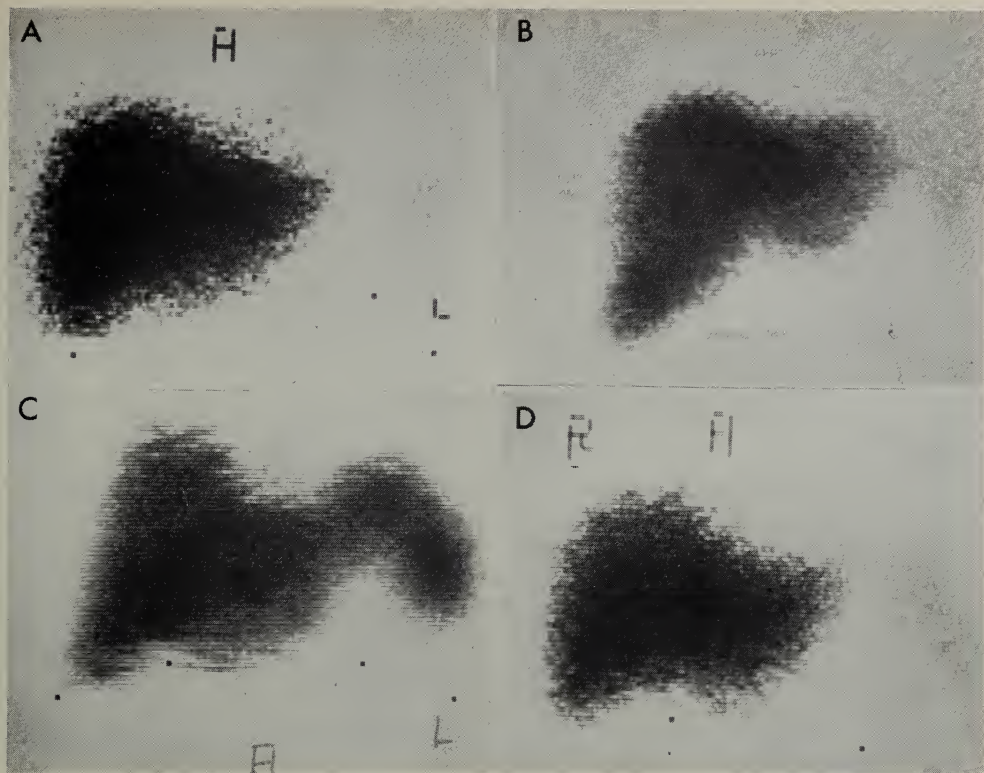


Figure 5.—Commonly encountered scanning configurations of the normal liver and spleen. Note that the spleen is usually not seen clearly. *A*: Gold-198 scan. *B*, *C*, *D*: Technetium-sulfur suspension scans; note prominent left lobe in *B* and clearly visualized spleen in *C*.

involved and destroyed it, especially if the presence of a mass in this region were confirmed radiographically or by physical examination.

Rose bengal can yield unique information for the diagnosis of obstructive jaundice. Upon ingestion, rose bengal is picked up by the parenchymal cells of the liver, excreted in the gallbladder, and then, if all is normal, passes out into the gastrointestinal tract to the duodenum. This excretion sequence is prevented by an obstruction. The rose bengal will be picked up by the liver, if the liver still has this capacity, but then the agent will gradually be released by the liver into the bloodstream, to be eventually excreted through the kidneys.

Figure 8 illustrates the usefulness of the rose bengal liver scan. There is essentially no uptake of technetium-sulfur colloid (Figure 8A) in the Kupfer cells of the liver. In the particular case

illustrated the liver function was so impaired because of obstructive disease that most of the colloid is picked up in the spleen, the bone marrow, some in the liver, and some in the phagocytes of the lungs. Figure 8B shows a rose bengal scan in the same patient. The tracer is picked up initially in the liver and in the gallbladder, which is seen clearly; much of the tracer is then passed into the gastrointestinal tract, and a good deal of it can be seen in the bowel. This is a diseased liver, but there is no evidence of actual obstruction, although there is no question that the capacity to pick up a tracer such as technetium-sulfur colloid is much impaired.

Pancreatic scanning, in practice since about 1962, is based on the labeling of methionine (a precursor to pancreatic enzymes) with radioisotopes. An uptake in the pancreas (Figure 9) can be seen in about 50 percent of the cases given the labeled methionine. If an uptake looks rela-





Figure 6.—Liver scan (technetium-sulfur colloid) showing questionable area of decreased tracer uptake in the hilar region, representing destruction of functioning liver tissue.

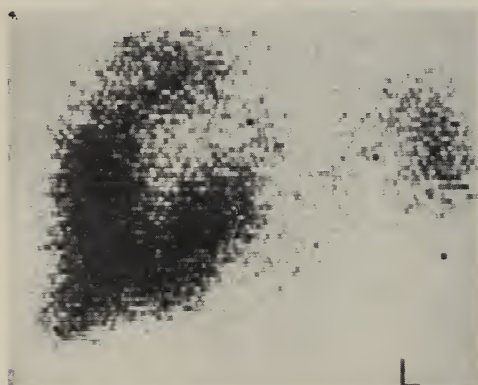


Figure 7.—Liver scan (technetium-sulfur colloid) showing destruction of the left lobe and of a portion of the right lobe due to malignancy.

tively normal in concentration and configuration (taking into account that we are in a very early stage in the understanding of the variations of the pancreas in man) the chances are that the organ is normal. On the other hand, failure to visualize it or the presence of areas of no uptake is a good indication of some problem with the pancreas. This is not a widely accepted technique; I think it has promise for the future. Some investigators have claimed it to be as good as angiography of the pancreas, but that, of course, depends upon the capability (and luck) of the person doing the angiography. Scanning is, however, nontraumatic and can be done with relative ease compared with current angiographic techniques.

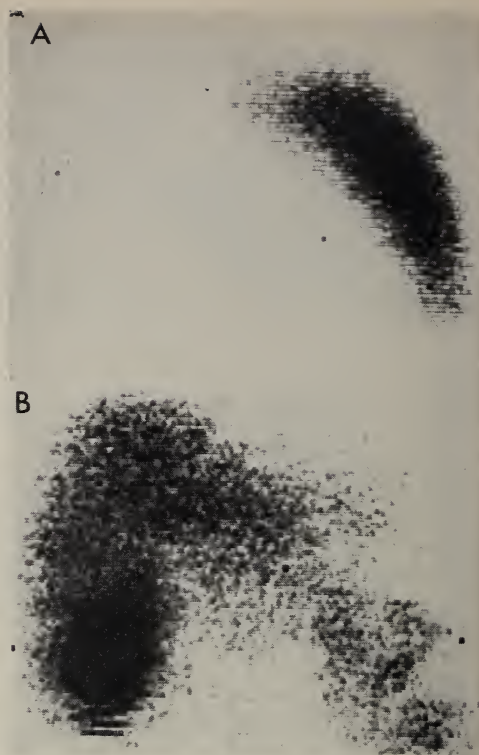


Figure 8.—*A*: Liver scan (technetium-sulfur colloid) showing no particulate uptake in the liver Kupfer cells, but only in the phagocytes of the spleen. *B*: Rose bengal scan on same patient, showing functioning of the parenchymal cells and discharge of the tracer into the gastrointestinal tract.

## Transjugular Transhepatic Cholangiography

DR. MARTIN A. POPS (Department of Medicine): To start with an oversimplification: in cases of obstructive jaundice, the obstruction is surgically amenable where it resides exterior to the liver. But the clinical picture and laboratory tests can be identical to those obtained in cases where it is located within the liver, as it may be when cholestasis occurs secondary to infectious hepatitis or is caused by chlorpromazine or methyltestosterone. This has led in some instances to the mistaken performance of surgical operation in cases of cholestatic viral hepatitis, with great risk to the patient. Thus it is important to determine whether patients with apparent obstructive jaundice are surgically treatable.



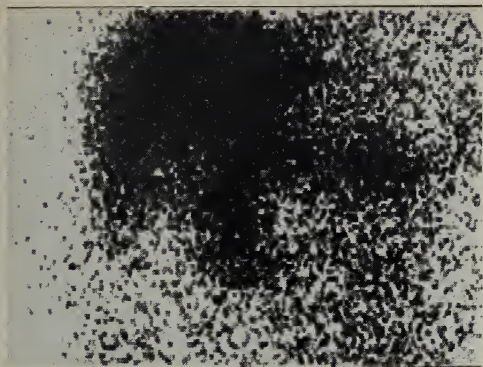


Figure 9.—Scan of the pancreas done with  $\text{Se}^{75}$ -labeled methionine.

The oldest technique (and the one that we still favor when possible) is visualization of the biliary tree by intravenous cholangiography. This depends on hepatic conjugation and excretion of an iodide introduced into the systemic circulation. With jaundice, however, liver function may well be compromised to the point where uptake and excretion of the opaque substance is suboptimal and visualization is not obtained. Direct cholangiography may then be considered. Three techniques are now in use.

The first method is, of course, to operate on the patient and do a cholangiogram at the operating table. Operative cholangiography has wide application, with obvious limitations. As our main topic is the preoperative evaluation of the jaundiced patient, we shall proceed to consider the other types of direct cholangiography.

*Transhepatic cholangiography* involves the injection of a dye directly into the biliary tree after lateral percutaneous puncture of the liver. The contrast agent fills the biliary system. In Figure 10, a gallstone totally occluding the common hepatic duct can be seen. The patient presented with jaundice and pruritus but no pain. The cholangiogram proved that in her case jaundice was amenable to surgical treatment.

Transhepatic cholangiography poses some problems, and the reports dealing with this method often stress the need for immediate surgical intervention should obstruction be found. One recognized complication is leakage of bile back through the hepatic puncture site into the peritoneal cavity, with resultant bile peritonitis.

The other reported complication of this pro-

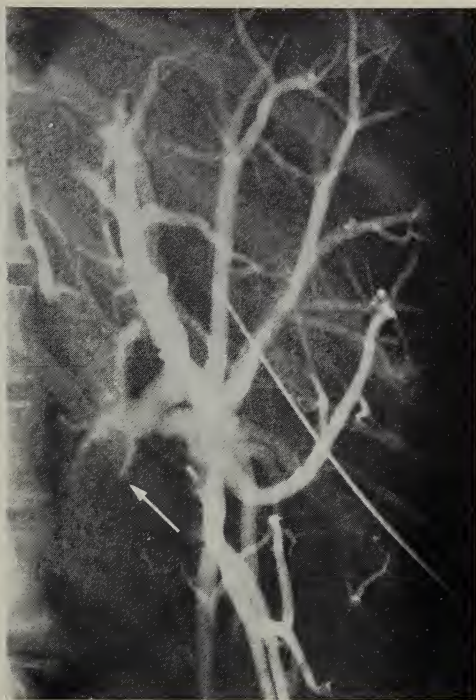


Figure 10.—Transhepatic cholangiogram demonstrating total occlusion of the common hepatic duct by calculus (arrow).

cedure is hemoperitoneum. In performing transhepatic cholangiography the liver capsule is being punctured from the outside, so to speak. Having created a situation where either bile or blood can extravasate into the peritoneal cavity, most persons experienced with this method would like to be sure that the operating room is ready in case ductal obstruction is found.

At UCLA, Drs. W. N. Hanafec and M. Weiner have recently devised a method of percutaneous cholangiography whereby the biliary system may be opacified without the necessity of hepatic capsule puncture. They found that straight-line access to the hepatic veins was obtainable by cannulation of the right internal jugular vein. A slightly curved long needle, adapted from trans-septal cardiac catheterization, can be passed into the liver via its venous system and thence into the hepatic parenchyma and finally into a biliary duct. The chances of successful visualization are, of course, increased if extrahepatic obstruction and secondary ductal dilatation are present. This technique may provide

an advantage over transhepatic cholangiography because the hepatic capsule is not punctured, thereby reducing or eliminating the risks of bile peritonitis and hemoperitoneum. Our experience over the past three years has tended to bear this out.

Figure 11 illustrates a transvenous (transjugular) cholangiogram done by the technique just described. It shows a common duct stricture in a man who presented with jaundice six years after cholecystectomy.

Figure 12 shows the radiographic studies in the case presented by Dr. Johnson. The upper gastrointestinal series shows some suggestive effacement and narrowing of the duodenal loop and some obliteration of the folds of the duodenum, suggesting a mass in the head of the pancreas. The cholangiogram reveals an enormously dilated intrahepatic ductal system. The arrow points to a sharp cut-off which we have come to recognize as characteristic of tumor. As was noted earlier, on surgical operation a fairly large carcinoma was found at the head of the pancreas.

Complications of transjugular cholangiography have included febrile episodes in several patients following the procedure and, in one case, frank Gram-negative sepsis with death. The threat of bacteremia and sepsis may be reduced by preprocedural preparation of the patient with appropriate antibiotics such as ampicillin or tetracycline. It would seem wise to employ antibiotics in this way, especially if there is history of episodes of cholangitis.

In summary, then, we have a new technique of direct cholangiography which may be very useful in diagnosis and planning of management for the patient with apparent obstructive jaundice. The complication of bile peritonitis and hemoperitoneum can be avoided, thus eliminating the necessity for immediate operation. The risk of bacteremia is probably the same or greater than with transhepatic cholangiography.

### Obstructive Jaundice in Infants

DR. ERIC W. FONKALSRUD (Department of Surgery): Although carcinoma of the head of the pancreas and choledocholithiasis are unusual in infants and children, jaundice is nonetheless a common and serious problem in this age group. Of particular clinical importance (as in adults) is the separation of obstructive from nonobstructive jaundice. Pathologic jaundice usually appears during the first 36 hours after birth. When jaundice



Figure 11.—Transjugular cholangiogram demonstrating severe stricture of the common hepatic duct (arrow).

persists beyond the second week of life, the likelihood is greater that it is of the obstructive type.

Obstructive jaundice may be identified by means of a combination of methods. The history and physical examination may indicate the possibility of the jaundice being caused by infection, isoimmunization, rubella, cystic fibrosis, or other non-obstructive conditions. The age at onset of the jaundice may be helpful in separating various types of nonobstructive jaundice, as is shown in Table 2, in which conditions are classified by whether jaundice first appeared before or after the seventh day of life. It seems that hepatitis in neonates is not an inflammatory condition similar to that in adults, but rather results from a congenital malformation of the hepatic cells.

Several conditions may produce nonobstructive jaundice in infants, with the onset of symptoms at various ages; these include conjugation deficiency, sepsis, concealed hemorrhage, galactosemia, spherocytosis, drug toxicity, and hypoxia. Jaundice may occur during the first week or as late as one or two months of age. Certain drugs



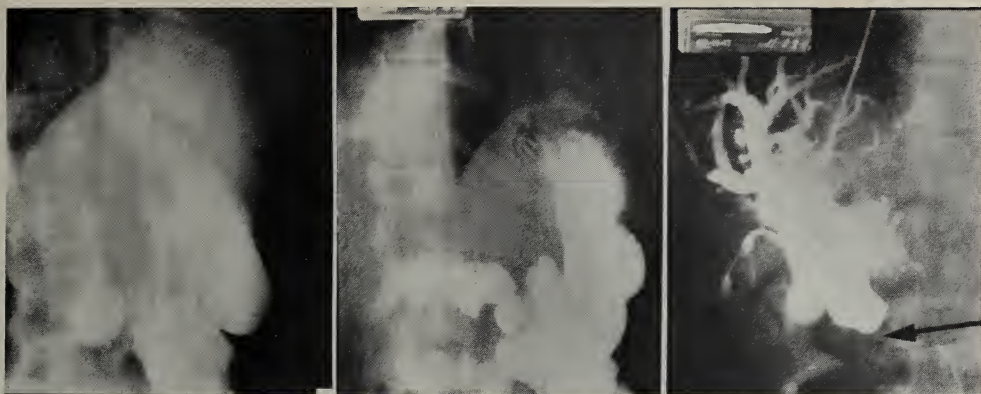


Figure 12.—*Left and center:* Upper gastrointestinal series showing suggestive effacement of the duodenal loop. *Right:* Transjugular cholangiogram demonstrating pronounced dilatation of intrahepatic ductal system; cutoff by tumor arising at the head of the pancreas is indicated by the arrow.

TABLE 2.—*Classifying Characteristics of Nonobstructive Jaundice*

Appears Under 7 Days of Age

Icterus neonatorum  
Isoimmunization (Rh and ABO)

Appears After 7 Days of Age

Hepatitis  
Toxoplasmosis  
Cytomegalic inclusion disease  
Congenital syphilis  
Familial nonhemolytic icterus  
Cystic fibrosis  
Pyloric stenosis

and sepsis may produce jaundice in an infant several months of age.

Various tests, such as the blood count, typing, Coombs' test, serology, urine galactose and examination for cytomegalic inclusion bodies, may be of help in identifying these causes of nonobstructive jaundice. Skull roentgenograms may identify toxoplasmosis as the cause of jaundice. The findings that are most helpful in the recognition of obstructive jaundice are acholic stools and biluria. An elevation in the direct serum bilirubin, absence of urobilinogen in the urine, and absence of I<sup>131</sup> rose bengal excretion into the intestine are confirmatory evidence for the presence of obstructive jaundice.

Several forms of obstructive jaundice may occur in small infants. Congenital biliary atresia is the most common type in neonates, the incidence being 1 in 2,000 to 3,000 births. This malformation may be present in a variety of anatomical patterns, from atresia of the entire ductal system to

either extrahepatic or intrahepatic ductal atresia. In the most commonly encountered form of this anomaly the extrahepatic ducts and gallbladder are atretic. In only a small number of infants does the intrahepatic ductal system empty into a dilated proximal extrahepatic duct which communicates with an atretic common bile duct. This is the only form of biliary atresia that may be corrected surgically by means of a choledochenteric anastomosis, although the eventual prognosis depends upon the degree of cirrhosis that develops before operation.

Biliary hypoplasia is an uncommon malformation in which either extrahepatic or intrahepatic bile ducts are narrowed in localized areas, producing partial ductal obstruction and jaundice, sometimes at an early age. This condition is believed by many physicians to be a variant of giant cell hepatitis with narrow ducts. Many children with biliary hypoplasia live until adolescence, although cirrhosis and portal hypertension usually become evident and are progressive.

Choledochal cysts may become clinically symptomatic in infants as well as in children or adults. This congenital dilatation of the common bile duct produces partial biliary obstruction with resultant intermittent jaundice, fever, pain, and usually an abdominal mass. Such cysts should be recognized early and drained internally before severe cirrhosis develops. This is one of the most readily correctable forms of obstructive jaundice encountered in pediatric patients.

Most children with biliary atresia die within



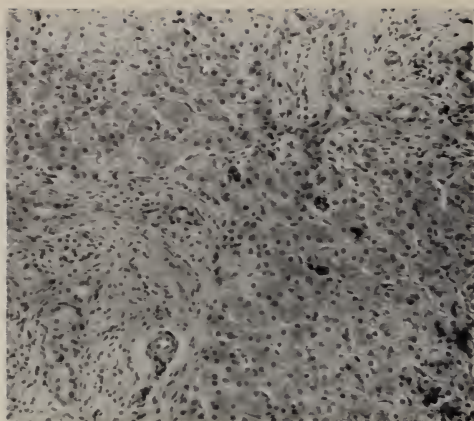


Figure 13.—Liver biopsy specimen from a 6-day-old infant with biliary atresia, showing moderate periportal fibrosis. This child subsequently underwent orthotopic liver homotransplantation and died with hepatic necrosis due to arterial thrombosis three weeks after transplantation.

the first two years of life (the average at 19 months), regardless of the type of therapy. Once the diagnosis is suspected and substantiated by the laboratory studies, a laparotomy with open liver biopsy is recommended. If the liver is firm, nodular and dark green, characteristic of biliary cirrhosis, the incision is extended and a thorough exploration of the hepatoduodenal ligament is undertaken in search of a dilated proximal duct, either extrahepatic or intrahepatic, which may be anastomosed to the small intestine. If the liver is soft, smooth and reddish brown, suggestive of hepatitis, a small catheter is placed into the gallbladder, and the wound is closed as quickly as possible to minimize the duration of anesthesia. A cholecystogram and cholangiogram are then performed with the patient awake. A well-visualized complete extrahepatic ductal system excludes the likelihood of biliary atresia. If the ductal system is not visualized and biopsy of a prepared specimen of liver is diagnostic of biliary atresia, laparotomy and extensive exploration of the biliary ductal system are subsequently performed. The importance of early biopsy and accurate identification of the occasional surgically correctable lesion early is emphasized by the case illustrated in Figure 13, which shows moderate cirrhosis in a specimen taken from an infant with biliary atresia at six days of age.

Because of the almost uniformly poor prognosis of children with biliary atresia, several experi-

mental approaches have been studied to reduce the hyperbilirubinemia. The use of corticosteroids and cholestyramine to reduce the serum bilirubin, which was mentioned earlier in discussion of the management of adults with jaundice, has been of some value in infants with jaundice. Clinical attempts to reduce the serum bilirubin which is in equilibrium with lymph by external drainage of thoracic duct lymph have resulted in massive protein and fluid losses that make the procedure unfeasible for more than short periods. One child with biliary atresia was kept alive for approximately three months with the continued use of this treatment. At UCLA we have modified this approach by anastomosing the large lymphatic channels in the hepatoduodenal ligament to an isolated loop of small intestine in five children with biliary atresia, hoping to cause excretion of excess bilirubin and yet allow intestinal absorption of proteins and fluid. Although these procedures may lower the serum bilirubin temporarily, there is little evidence to suggest that the progression of the biliary cirrhosis is altered, and death usually occurs at approximately the same age as when the condition is untreated.

Perhaps the greatest hope for the future management of children with biliary atresia rests in liver homotransplantation, which has become increasingly successful during the past several years, and has been used in three patients in this hospital.

### Sclerosing Cholangitis

DR. WILLIAM P. LONGMIRE, JR. (Department of Surgery): Sclerosing cholangitis is, fortunately, a rare disease and no one has a wide experience with it from which to draw specific conclusions. One of the largest series reported in the literature at this time concerns 42 cases collected by Warren and his associates<sup>20</sup> at the Lahey Clinic; the authors point out the almost uniformly unfavorable results of this disease.

There are two points that I would like to make in regard to this process, usually diagnosed at the time of operation for jaundice of an obstructive type in which a decided thickening and sclerosis of the wall of the common duct is found, a change that occurs in the submucosal layer with pronounced periductal inflammatory reaction about it. The extent of the condition may vary from a very mild sort of process to one that almost completely obliterates the lumen of the duct.

First, one must differentiate this process from

a primary bile duct carcinoma, and this can present some major problems, primarily because when performing a biopsy of the wall of the common duct the surgeon never likes to remove a really significant portion of the duct for fear of creating a permanent biliary fistula; hence the specimen that the pathologist frequently receives is not adequate to reach a definitive diagnosis.

Nevertheless, there are several points that can be made with regard to this differential diagnosis. In the first place, when dealing with sclerosing cholangitis, this is usually found to be a diffuse process that is apt to involve the entire extrahepatic biliary system. Not infrequently, changes will also be found inside the liver which are compatible with a primary biliary cirrhosis, or what we refer to as cholangiolitic hepatitis (to be further discussed later on).

On the other hand, in the case of carcinoma an operative cholangiogram will demonstrate a more localized area of constriction, and above that point of constriction a dilatation of the intrahepatic ductal system or a dilatation of some portion of the extrahepatic system if the process is localized to the lower portion of the duct. The point is that the sclerosing cholangitis is apt to be a diffuse process and the carcinoma apt to be localized, with dilatation above the point of obstruction in the case of carcinoma, and no dilatation above with the cholangitis.

As occasional exceptions to this, there are patients with a localized process, and these account for the rare case of sclerosing cholangitis in which some permanent cure may result.

In addition to this process alone, sclerosing cholangitis may also occur in combination with some other systemic diseases. Not infrequently, it occurs with ulcerative colitis, with retroperitoneal fibrosis, with sclerosing fibrosis in other anatomical sites; its relationship with these other diseases is not clear.

The other major point I would like to establish is that this is probably the same process that we identify as cholangiolitic hepatitis or primary biliary cirrhosis, affecting in this case first or most severely the extrahepatic portion of the biliary tract.

Cholangiolitic hepatitis occurs typically in the most proximal portion of the biliary secretory unit, while sclerosing cholangitis occurs more often in the major or extrahepatic ductal system. These processes frequently overlap. For example, in four

of the 28 cases of cholangiolitic hepatitis that we have reported<sup>6</sup> from this institution the patient was thought to have a normal extrahepatic biliary tract at the time of the first exploration, but at subsequent exploration, a year or more later, all four were found to have extensive thickening and sclerosis of the extrahepatic system as the process seemed to extend. Turning the story around, practically all the patients reported upon by Warren and his associates<sup>20</sup> eventually died of biliary cirrhosis, so that there was an extension of the process along this line.

In relation to this disease and ulcerative colitis, 12 of the 42 patients in Warren's report had ulcerative colitis in association with the bile duct disease. Two of these patients made an excellent recovery, but ten did poorly, and five of them died of the disease. In nine of these ten patients biliary cirrhosis developed.

Sherlock<sup>16</sup> said that colectomy and antibiotics are of no benefit in the treatment of this particular type of disease; we therefore feel that this is probably not an infectious process but rather a systemic disorder of some type, possibly related to an immune or an allergic phenomenon. It is associated frequently with other disease processes of similar nature. It follows a rather unfavorable course in a majority of instances, and the various treatments of prolonged biliary drainage are probably ineffective in the majority of cases. Such treatment is possibly contraindicated, inasmuch as it provides a means or an avenue for secondary infection to enter and extend up the biliary tract. The use of steroids may be of some value in the very early cases if diagnosis can be made, and a short course of therapy along this line may be tried.

## Discussion

DR. CLARKE: We have a few minutes for questions and discussion. First, I would like to say that we are delighted to have Professor Richard Welbourn from Hammersmith with us this month as a visiting professor in the Department of Surgery. I would like to invite Professor Welbourn to comment if he wishes.

DR. RICHARD WELBOURN (Royal Postgraduate Medical School of London, Hammersmith, England): I have been fascinated to listen to these papers on the diagnosis of obstructive jaundice. The liver scanning interested me very much. It is something which we, too, are doing; and, like you,



we are perhaps groping a bit in the early stages and not knowing what particular appearances really indicate.

The transjugular transhepatic cholangiography I found particularly interesting. I had not heard about this before. I shall certainly tell our radiologists at home about this, and ask them if they can help us, for it would be helpful in the type of patient on whom we now would have to do a puncture through the skin from the outside; and these procedures, of course, have to be done on the way to the operating theater, and not all these patients may need operation.

DR. SHERMAN M. MELLINKOFF: I wonder if I could ask Dr. Rösch if there is a characteristic appearance of the angiogram in cholangiolitic hepatitis or sclerosing cholangitis.

DR. RÖSCH: There are changes secondary to periportal infiltration, liver enlargement or liver atrophy, and cirrhosis; but there is no typical angiographic appearance of sclerosing cholangitis.

DR. LONGMIRE: I would like to ask Dr. Johnson why the bypass operation did not cure the jaundice in the case presented.

DR. JOHNSON: I could not tell from the chart. I do not know.

DR. LONGMIRE: It seems to me that there might be two possibilities. One is that the gallbladder was used in the decompression, and the tumor may have involved the junction between the cystic and the common ducts, thereby obstructing the channel of decompression; such a tumor extension frequently occurs and is one of the reasons that a cholecystojejunostomy is often not a satisfactory operation for decompression. The other explana-

tion would be that intrahepatic disease was so extensive that the patient's jaundice would not be relieved even though the extrahepatic ducts were decompressed.

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# Important Advances in Clinical Medicine

## *Epitomes of Progress -- Radiology*

*The Scientific Board of the California Medical Association presents the following inventory of items of progress in Radiology. Each item, in the judgment of a panel of knowledgeable physicians, has recently become reasonably firmly established, both as to scientific fact and important clinical significance. The items are presented in simple epitome and an authoritative reference, both to the item itself and to the subject at a whole is generally given for those who may be unfamiliar with a particular item. The purpose is to assist the busy practitioner, student, research worker or scholar to stay abreast of these items of progress in Radiology which have recently achieved a substantial degree of authoritative acceptance, whether in his own field of special interest or another.*

*The items of progress listed below were selected by the Advisory Panel to the Section on Radiology of the California Medical Association and the summaries were prepared under its direction.*

Reprint requests to: Division of Scientific and Educational Activities, 693 Sutter Street, San Francisco, Ca. 94102

### Perinatal Pulmonary Roentgenography

Since 1960 increased utilization of radiographic examination of the newborn chest has played an important role in the recognition of three new syndromes of newborn pulmonary disease:

1. Bronchopulmonary Dysplasia — This syndrome is characterized by a history of severe hyaline membrane disease treated with prolonged artificial ventilation and high concentrations of supplemental oxygen and a radiologic picture of focal hyperexpansion of the lungs.

2. Wilson-Mikity Syndrome — This relatively late arising chronic pulmonary disease in very low birth weight premature infants is also characterized

by a radiologic picture of focal hyperexpansion of the lungs. A history of artificial ventilation is not present though the administration of low concentrations of supplemental oxygen is frequent. Because of the similar radiographic picture, common etiologic factors are postulated to be present in Bronchopulmonary Dysplasia and Wilson-Mikity Syndrome.

3. Transient Tachypnea of the Newborn — This disorder mimics mild congestive heart failure in the immediate newborn period with radiographic changes characteristic of pulmonary vascular congestion and interstitial edema. Clinical evidence of congestive heart failure is not present, and as its name implies, all findings clear in one

to five days without therapy. The postulated etiology for this syndrome is a disorder in the absorption of fluid from the lung at birth.

WILLIAM H. NORTHWAY, JR., M.D.

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### Posterior Fossa Aneurysm Presenting as Mass Lesions

Aneurysmal dilatations may frequently reach tremendous proportions in the posterior fossa without evidence of rupture, closely simulating expanding tumors. Since ventriculography is frequently considered the procedure of choice for the diagnosis of posterior fossa tumors, misleading and even disastrous information may result. Ectasias of the basilar artery rarely rupture and may present with clinical symptoms simulating pontocerebellar angle tumors as well as intrinsic pontine glioma lesions. Vertebral angiography will demonstrate aneurysms of the basilar artery as well as the posterior inferior cerebellar arteries.

WILLIAM N. HANAFEE, M.D.

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### Genus Varus and Valgus in Children

A wide variation of normal was found by observing two groups of infants and children. Three hundred twenty-two children from a Well Baby Clinic were followed and compared with 61 children who were considered to have pathologic changes by clinical examination. From periodic roentgen examination, striking features could be observed.

Bowed legs before the age of 2 years and knock-knees between the ages of 2 years and 12 years are clearly established as normal growth patterns in otherwise healthy children. The patients referred with clinical diagnoses of bowed legs and knock-knees fell within the normal range of varoid to valgoid growth patterns.

Pathological varus and valgus deformities do occur, but they were only seen secondary to clubfoot, neurological disease, osteogenesis imperfecta, and obesity.

Treatment for any type of bowed legs or knock-knees in a healthy child is not indicated.

WILLIAM N. HANAFEE, M.D.

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### Multiple Progressive Intracranial Arterial Occlusion of Children and Young Adults

A syndrome of children and young adults, hemiplegias developing during infancy and childhood are due to occlusions of the internal carotid artery system. The cause may be embolism, infection, trauma, or a localized arterial lesion. Cerebral angiography is now readily performable in infancy and gives a specific diagnosis. The children usually present with progressive paralysis, ushered in by convulsions, twitching movements, speech disturbance, unsteady gait, and headache. Mental retardation occurs in about a third of the children.

Angiographically, anastomotic channels between the external carotid system and the internal carotid artery can be identified as well as collaterals between leptomeningeal branches of the internal carotid artery system. Anastomosis may be visible from the vertebral system to the internal carotid artery system or vice versa.

The disease usually progresses to total occlusion of the major vessel, but collaterals may dilate so that the patient may recover with little residual motor or sensory disturbances. This entity is quite distinct from congenital hemiplegia.

WILLIAM N. HANAFEE, M.D.

#### REFERENCE

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## Spontaneous Closure of Acute Traumatic Renal Arteriovenous Fistulas

Acute traumatic arteriovenous fistulas of the kidney are a common injury resulting either from blunt trauma or penetrating renal wounds. Selective renal angiography is employed for the precise anatomic demonstration of these lesions early in the care of the patient.

Angiographic documentation of the spontaneous closure of acute traumatic renal arteriovenous fistulas was obtained in five patients who were managed conservatively and reexamined angiographically one to eight months following injury. This recently acquired understanding of the natural history of the lesion tends to negate the accepted surgical concept of early aggressive action designed to obliterate such lesions before the onset of significant secondary cardiovascular complications. At present it would appear that surgical intervention can safely be held in abeyance to permit a period of clinical observation in many instances.

MORDECAI HALPERN, M.D.

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## Renal Vein Thrombosis

Sudden, complete occlusion of the renal vein usually produces the classical picture of flank pain, fever, hematuria and proteinuria. Excretory urography reveals an enlarged kidney with absence of function, or delayed opacification of a compressed, stretched pelvo-calyceal system and sometimes ureteral notching by collateral veins. Less abrupt or incomplete occlusion produces less severe clinical and radiographic findings. In infants, dehydration is the usual cause of thrombosis; in adults, tumor, ascending thrombophlebitis, trauma and nephritis are frequent precursors. Differentiation from nephrosis can be difficult and important. Renal arteriography shows stretched interlobar arteries, a prolonged nephrogram, and dense, bulging pyramids. Cavography and renal venogra-

phy demonstrate the site and extent of obstruction, but are not without the hazard of dislodgement of thrombi.

FRANK A. BROWN, M.D.

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## Adrenal Venography

Adrenal venography is a useful supplementary technique for the demonstration and evaluation of adrenal tumors. Selective catheterization of the veins follows percutaneous insertion into the right femoral vein, and permits sampling of blood for hormonal assay as well as angiography. The right adrenal vein is approached directly from the inferior vena cava, the left by way of the left renal vein. Avascular tumors as small as 1 cm in diameter can be detected with this procedure. The complication of thrombosis and adrenal necrosis can be avoided by careful manual injection under fluoroscopic control.

FRANK A. BROWN, M.D.

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## The Roentgenologic Diagnosis Of Lactase Deficiency

Deficiency of the intestinal enzyme lactase is now believed to be the most common abnormality of the small bowel in man. It occurs in 5 to 10 percent of the white population and in more than 70 percent of non-whites. The symptoms of the disease are produced by the osmotic effect of the undigested lactose which draws water into the bowel lumen. Gas and lactic acid are also produced by bacterial action of the sugar. This excess fluid and gas causes cramps and diarrhea.

The abnormality can be diagnosed by an insufficient blood glucose rise after an oral lactose tolerance test. Recently roentgen screening methods have been described for the detection of this en-



zyme deficiency: 50 grams of lactose are mixed with the barium solution used for a small bowel examination. Serial roentgenograms are taken in the usual way. In the presence of lactase deficiency, characteristic radiographic changes occur with dilatation of the distal small bowel and pronounced dilution of the barium. This dilution effect is even more striking in the colon, where barium is usually concentrated by water resorption. Rapid transit is also characteristic and the patients with this disorder usually report cramps and diarrhea during the examination.

DOUGLAS J. SHEFT, M.D.

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### Selective Arteriography in Locating The Site of Gastrointestinal Hemorrhage

Bleeding into the gastrointestinal lumen at a rate as low as 0.5 ml per minute (360 ml per 24 hours) can be demonstrated by selective visceral arteriography. Wide clinical experience has now established arteriography as an important technique in evaluation of gastrointestinal bleeders. In addition to demonstration of active bleeding, arteriography can establish the direction of blood flow in the portal system, and the presence of a variety of vascular, neoplastic, and inflammatory lesions serving as a source of chronic or recurrent bleeding.

KEVIN G. RYAN, M.D.

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### Splanchnic Artery Stenosis and Occlusion

On review of more than 700 splanchnic artery angiograms a 17.3 percent incidence of occlusion of single or multiple vessels was noted. The majority of these investigations were for hypertension, peripheral vascular disease, or abdominal

masses. The celiac artery was more frequently involved with non-arteriosclerotic lesions such as fibromuscular hyperplasia, impression of the crus of the diaphragm, or adhesive bands. The superior mesenteric and inferior mesenteric arteries were more commonly affected by concentric narrowing of arteriosclerosis. None of the patients with eccentric stenosis exhibited typical abdominal angina despite severe stenosis and multiple vessel involvement. Surprisingly, 49 percent of the patients with obstruction of the celiac artery had abdominal symptoms attributable to the lesion.

WILLIAM N. HANAFEE, M.D.

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### Preliminary Sensitivity Testing In Intravenous Pyelography

Minor reactions to intravenous contrast media used in excretory urography occur rather commonly. These are generally mild and transient, and require no treatment. Rarely severe reactions occur requiring prompt treatment to prevent death or other serious consequence. No preliminary sensitivity testing procedure has been found to be absolutely reliable for excluding those patients who will experience either an untoward or an allergic reaction to the intravenous iodine-containing contrast medium. Most radiologists perform a preliminary sensitivity determination of some kind, usually the intravenous injection of a small volume of the contrast medium. A history of clinical allergic disease, sensitivity to iodine, or an untoward reaction to the previous pyelogram injection should alert the physician to a greater possibility of reaction to the injection medium. Drugs and equipment to treat severe reaction promptly should be readily available. Prophylactic treatment with steroids or antihistamines may be required if the examination is absolutely necessary and the patient has a known allergic response to the contrast medium.

A. J. PALUBINSKAS, M.D.

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## Hypotonic Duodenography

Studies using pharmacologic agents to alter gastrointestinal physiology are extending the potential of diagnostic roentgenology. A fertile field of exploration has been the duodenal loop. This area has always been difficult to examine and, because of spasm or rapid peristalsis, subtle changes reflecting a disease process in the adjacent pancreas may be missed. Hypotonic duodenography, by inducing temporary paralysis with the anticholinergic drug propantheline bromide, allows a detailed demonstration of the anatomy of the duodenal loop.

Tubeless methods were used for many years. Recent methods involve intubation of the duodenum, followed by the administration of 60 mg of propantheline bromide by intramuscular injection. This gives effective atony for about 20 minutes. The duodenum is then distended with barium and air under fluoroscopic control.

Urinary retention is occasionally a problem, so the procedure should be done with caution in the presence of prostatic enlargement. Glaucoma is also said to be a contraindication. A dry mouth, some pupil dilatation, and blurred vision or tachycardia are other effects of the drug.

Signs of abnormality on hypotonic duodenography such as effacement or spiculation of the mucosa are similar to ordinary gastrointestinal roentgenographic studies, except these signs tend to be accentuated and more reproducible.

DOUGLAS J. SHEFT, M.D.

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## Percutaneous Transtracheal Bronchography

The transcricothyroid approach to the tracheo-bronchial tree provides a convenient, safe and relatively comfortable technique for bronchography. The simplest method is use of the intracath used commonly for venous cannulation. After the skin has been anesthetized, the needle of the intracath is inserted through the cricothyroid membrane. The polyethylene tube is then passed into the trachea and either or both bronchial trees may then be opacified with oily dionosil.

A refinement of the method involves use of the Seldinger technique. After introduction of the needle, a soft flexible guide wire is passed through the needle into the trachea. The needle is removed and a catheter is inserted over the guide wire. Bronchi may then be selectively catheterized with the aid of preshaped tips, tip control devices or magnetic tip control.

HOWARD M. LEVINSON, M.D.

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## Contrast Laryngography

The contrast laryngogram has proved itself a valuable addition to the armamentarium in both diagnostic and therapeutic radiology. After premedication with atropine, topical anesthesia of the hypopharynx is accomplished by spray or inhalation nebulizer. A long metal cannula is placed on the dorsum of the tongue, and approximately 10 ml of oily contrast material is slowly dripped into the hypopharynx. Fluoroscopic spot films are then made in antero-posterior and lateral projections with the patient erect. Exposures are usually made during inspiration, phonation, Valsalva and modified Valsalva maneuvers. Detailed view of hypopharyngeal and laryngeal anatomy is routinely obtained. The procedure is of the greatest value in the clinical staging of hypopharyngeal carcinoma, but also is helpful in cases of laryngeal trauma. It is particularly valuable in evaluating the subglottic space, which is difficult to assess even with direct laryngoscopy.

GEORGE R. LEOPOLD, M.D.

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## Pulmonary Leiomyoma

The world literature has a total of 21 proved cases of pulmonary leiomyoma, and it is a seldom considered histologic diagnosis in cases of a pri-

mary lung mass. Sweets recently reported a case of a 3 cm right lower lung solitary nodule in a 21-year-old asymptomatic male. Isotope scanning of the lung and selective pulmonary arteriography were of no diagnostic value, and at thoracotomy the lesion was well encapsulated and completely resectable.

As a rule, these lesions are totally asymptomatic, fortuitously discovered, and histologically completely benign.

Reviewing the literature of all known reported lesions, Sweet noted they characteristically are slow in growth and infrequently calcified. They may be endobronchial or intraparenchymal.

ROBERT H. REID, M.D.

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### Frequency of Urinary Tract Abnormalities in Sickle Cell Disease

Renal medullary structural damage from sickling with stasis and infarction often results in bilateral caliectasis and poor concentration of contrast media by the kidney (isosthenuria).

Caliectasis not related to the presence or the absence of urinary tract symptoms was found in 7 of 17 cases. No cases of unequivocal renal papillary necrosis were found. Intravenous drip technique provides decidedly improved opacification of the renal collecting system and should be utilized routinely in patients with sickle cell disease.

GEOFFREY A. FRICKER, M.D.

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### Rapid Sequence IVP in Hypertension

A simple modification of the routine intravenous pyelogram has found universal acceptance in the examination of patients suspected of having renovascular hypertension. The modification consists of the inclusion of several time-spaced films of the kidneys within the first several minutes after

the rapid injection of the pyelographic medium. Particular features searched for on such hypertension pyelograms are differences in the size of the kidneys, their calyces, and the appearance time and concentration of the excreted opaque. False positive and false negative results occur, and there are screening procedures that are said to be more accurate. However, the simplicity of the rapid sequence IVP and its universal availability continue to make it the most widely used radiologic screening procedure in the examination of unexplained hypertension.

A. J. PALUBINSKAS, M.D.

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### Radionuclide Studies of Pulmonary Ventilation and Perfusion

A complete evaluation of regional lung function should include examination of both the distribution of air throughout the lungs as well as the perfusion of blood to the lungs. By using modern radionuclide imaging techniques, alterations in the normal patterns of regional ventilation and perfusion often can be demonstrated before pathologic changes are recognized on standard chest radiography.

Radionuclide studies of lung perfusion can be accomplished either by injecting radioactive labeled particles (10 to 60 microns) intravenously or by a more central injection of a radioactive inert gas such as xenon-133 dissolved in saline solution. The resulting image of the distribution of these materials in the lung, as recorded with a device such as the scintillation camera, indicates the relative regional perfusion of blood. Regional ventilation is evaluated by having the patient breathe a mixture of air containing a small quantity of xenon-133 gas. Comparison of the perfusion lung scan, or picture of blood flow, with the image of ventilation permits effective study of early changes associated with almost all types of pulmonary disorders. These techniques have been most valuable in patients suspected of having pulmonary embolization, chronic bronchitis, emphy-



sema, lung cysts, unexplained hemoptosis, bronchial obstruction resulting from tumors and in the preoperative and postoperative evaluation of patients undergoing thoracic surgical operation.

WILLIAM L. ASHBURN, M.D.

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### Intravenous Pyelography in Azotemia

Renal failure, in the absence of concurrent liver disease, is not a contraindication to excretory urography. Although the detail of renal structures obtained may be poor, the information gained can be vital, particularly the exclusion of remediable obstructive uropathy as the cause of the kidney failure. Standard volumes of any of the readily available intravenous urographic contrast media can be used, but larger volumes are recommended. Such high volume studies, particularly in combination with kidney tomograms and delayed x-ray films of the abdomen, can result in unexpectedly good demonstration of renal structures, even in some severely azotemic patients.

A. J. PALUBINSKAS, M.D.

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### Translumbar Pyelography in Children

When excretory urography fails to delineate the cause of unilateral obstructive uropathy and when retrograde pyelography is impossible, percutaneous translumbar pyelography may yield vital information. This procedure, utilized in 139 patients over the past 15 years, was reported from Stockholm in 1965.

Under television-monitored, image-intensification fluoroscopy, the dilated renal pelvis is punctured with a 20-gauge lumbar puncture needle. A urine specimen may be aspirated through this

needle for bacteriologic and cytologic studies, and then water-soluble contrast media is injected.

Recently, Lalli applied this method in four children who had congenitally obstructed ureters. There was no complication in this pediatric series and the study clearly delineated the nature of the obstruction.

CHARLES A. GOODING, M.D.

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### The Osteochondroses

It is now commonly accepted that most if not all of what has been termed osteochondrosis or osteochondritis dissecans is the result of trauma. Frequently the inciting incident will not be recalled by the patient and development of symptoms may be long delayed. Minor repeated traumatic events may provide a fitting cause for most of these lesions, but several features seen occasionally are still unexplained. These include bilaterally symmetric lesions, such as are sometimes seen in osteochondritis dissecans, familial occurrence, and multiple areas of involvement in a single patient. It is possible that certain persons have an altered response to minor osteocartilaginous trauma. At present it seems more appropriate to denote these conditions as transchondral fractures rather than infer a factor of avascular necrosis.

M. B. OZONOFF, M.D.

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### Growth Lines

Transverse lines in the metaphyses of the long bones have been termed "growth lines" but are more accurately denoted "post-growth arrest lines." Simple slowing or cessation of growth will not produce these bone strata, as they are formed only after recovery from illness when a spurt of growth is instituted. If growth is not resumed, a lucent line will be seen just beneath the cortex instead. This lucency was formerly thought to be

pathognomonic of leukemia but is now recognized as a sign of any chronic illness with bone growth retardation.

Growth lines can often be correlated with a definitely marked illness but there is no good correlation with the severity of the illness, for often severe illnesses leave no such marks. Conversely, many children will show growth lines during a period in which no cessation of growth or illness can be documented.

M. B. OZONOFF, M.D.

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### Congenital Bone Lesions Following Fetal Viremia

The longitudinal striations seen in the metaphyseal portions of some long bones in rubella syndrome are now thought to be due to damage to the fetal mesoderm with failure of subsequent maturation to osteoblasts. Consequently, columns of defective bone are formed which appear roentgenographically at birth as longitudinal, vertical, lucent striations. They are most common in the humeri and femurs. They usually disappear through remodeling in a few months.

These lesions were originally reported only with rubella syndrome, but recently reports have documented identical lesions in cytomegalic inclusion disease.

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- Reed GP Jr: Rubella bone lesions. *J Pediatr* 74:208-213, 1969

### Cerebrospinal Fluid Dynamics Studied With Radionuclides

Human serum albumin tagged with iodine-131 is currently being employed to evaluate the cerebrospinal fluid spaces in a number of neuro-

pathologic conditions including communicating hydrocephalus, CSF rhinorrhea and otorrhea, arachnoidal cysts and other obstructing lesions resulting from a variety of causes. The albumin tracer is injected in radionuclide cisternography via a lumbar puncture and the upward flow and symmetrical distribution of the tracer over the brain surface is observed.

Evaluation of the interventricular flow of the CSF is accomplished by injecting the radioactive tracer directly into the ventricular system in a manner similar to that used in air ventriculography. In addition to demonstrating altered flow caused by obstructing lesions, radionuclide ventriculography is ideally suited for evaluating the patency of neurosurgical shunts, particularly in children, where shunt revision is occasionally necessary. Shunt patency can also be examined by injecting the tracer directly into the subcutaneous pump of many of the currently used ventriculo-vascular shunts.

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### Isotope Lung Scanning In Pediatric Respiratory Disease

Although lung scanning with isotopes is a well established diagnostic procedure, its use has been greater in adults than in children, and particularly helpful in evaluation of pulmonary infarcts. Pendarvis and Swischuk presented a well-structured multi-method analysis of respiratory diseases in childhood utilizing the short half-life isotopes of indium, 113 iron hydroxide and the gamma camera scanning equipment. In addition to the isotope scanning, conventional radiography, arteriography and bronchography were used in each case.

Among conditions studied and reported were primary pulmonary artery anomalies, chronic respiratory disease such as tuberculosis, hilar and mediastinal masses, bronchiectasis, cystic fibrosis and congenital bullae.

Although isotope scanning is not a primary absolute diagnostic procedure, it is emerging in pediatrics as an increasingly useful correlative

study and may one day substitute for pulmonary arteriography and bronchography in selected cases.

ROBERT H. REID, M.D.

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### Radionuclide Angiography

Using modern high speed radionuclide cameras, it is possible to record the passage of radioactive substances through the vascular spaces. The resulting images do not provide the same degree of fine detail available with radiographic contrast angiography, but there are certain advantages in using radioactive compounds. The volume of the administered bolus is rarely more than 1 ml, allowing the injection to be made in an ordinary

syringe either through a selective catheter or, more often, by a simple venipuncture. No toxic effects or untoward reactions have been reported with these isotonic and physiologically inactive solutions and this safety has permitted evaluation of major vessels more routinely. Clinical uses for this technique have included evaluation of cerebrovascular occlusions, screening for large aortic aneurysms, unilateral early signs of renal transplant rejection, arterial and venous obstructions of major vessels such as the superior vena cava syndrome, and the study of certain types of acquired and congenital heart disease.

WILLIAM L. ASHBURN, M.D.

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# RELEVANCE



## today and tomorrow in Medical Education

### A FORUM WITH A PURPOSE

*Students of today question the relevance of much of their formal education. In medical schools the concern is particularly with the relevance of the educational experience to the professional commitment in modern society. To engender discussion of the subject, CALIFORNIA MEDICINE in its January issue printed eight essays by authors known to have keen interest in the subject.*

*Readers in California and elsewhere are invited to take part in a continuation of the forum in succeeding issues. The following are contributions selected from those received to date. Others will be published in the months ahead. At an appropriate time the material will be collated and, if feasible, the distillate will be prepared in the form of a statement.*

*If you have thoughts on the subject, just address them to the editors of CALIFORNIA MEDICINE, 693 Sutter Street, San Francisco, California, 94102. Keep your essays short, please.*

#### HERBERT A. HOLDEN, M.D.

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Immediate Past President, Alameda-Contra Costa  
Medical Association; Past President, California  
Academy of General Practice (1967)*

WRITING AS A general-practice physician some 25 years out of medical school I see much merit in the modern student's demand for relevance in medical education. By relevance I interpret the student to mean a very practical approach to health care and disease prevention. He is talking of active involvement in community health and social problems and also the promotion of an optimal environment, all for the preservation of health.

His attention has been focused on the unmet needs of both our rural and urban areas and he envisions himself as an important instrument in meeting that need. Let us hope that he does not lose that vision but prepares himself to be a crusader for social and medical reform, while he maximizes his involvement by becoming a front line, primary-contact physician. In such a capacity he can fill one of society and medicine's greatest needs.

To keep the student's enthusiasm for this type of medical involvement alive our medical schools should accede to his demand for community involvement during his academic years. This can be done by encouraging his active participation in local public health agencies, community clinics, private physician's offices as a preceptee, local medical society committees as an observer and participant, and in local private and public hospitals outside the medical school environment. Such wide exposure for the student and similar extensive involvement of the community in the medical school should be beneficial not only for the student, but also for all those who participate with him—namely, the university, the public community as a whole, and the local medical community in particular.

With such a joint effort by the medical school and the practicing physicians of the community the latter will find themselves drawn back into the influence of the university. In order to participate in the training of students they will find their need for and their desire to avail themselves of continuing medical education stimulated.

In discussing continuing education again I would emphasize the word "relevance." The busy physician is especially interested in information which he can use the next day or the next week in his own office or hospital. The more practical a postgraduate course the more popular. The practicing physician also wants training in modern timesaving devices, which may help him meet the time demands of his practice. He desires information regarding sophisticated techniques of data processing and the computer analysis of laboratory and diagnostic problems. The mechanization of practice seems to offer the only solution to meeting the increasing volume of patient needs. Experimentation with and the study of new methods in the delivery of health care is an area which has not been adequately emphasized by our teaching institutions.

Finally, teaching and learning methods must keep pace with the growing mass of technical knowledge in the medical fields. Physicians must individually avail themselves to speed reading skills and improve their learning habits through the use of audio and video tapes as learning aids. Educators similarly must continually explore new teaching methods such as programmed instruction, self-evaluation testing and similar devices to aid the student.

Such thought to the innovation of new techniques in teaching and learning with continual emphasis on the relevance of the material presented and the total involvement of not only the student and the university, but also the entire community will help meet the increasing demands made of medicine by modern society.

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THE OLD PROCESS of medical education was almost exclusively concerned with mastering clinical facts and basic principles. A technical proficiency in these areas is of course still mandatory, but it is an insufficient condition for a sound, modern professional education. In addition to technical training, the short period of formal medical education must also prepare students to cope with continuing and profound changes in society that affect the total health and well-being of patients.

In this sense, at least, a relevant medical education is one that tries to prepare students for the altered circumstances in which they will practice medicine for the 40 years after their supervised education is completed. How well we train students to avoid future obsolescence—both technical and societal—is the key to relevance. To do this, I believe, we must attempt to develop in students a *receptivity and sensitivity to postgraduate learning that will last them a lifetime.*

All the preceding articles in this Forum have the great merit of presenting incisive comments on three outstanding factors that define and determine relevance. In ascending order of importance, as I judge them, these factors concern the technical, practical, and sociological aspects of medical education.

There is probably no more striking evidence of the technical inadequacy of yesterday's undergraduate curriculum than the growth of the *Index Medicus*, which now annually contains over 200,000 entries. Surely none of us would contemplate practicing medicine without making use of some of the information represented by that figure—despite the benefits of our own "up to date" undergraduate education. There is no reason to doubt that technical information will continue to burgeon in difficulty and amount. As it does, will today's undergraduate be able to rely any more confidently on his "up to date" training than we were with ours?

But even if medical students are taught current facts and the techniques necessary to acquiring and evaluating future ones, ordinary medical care would not necessarily improve in a deep and fundamental way. Translating facts into *practical*, day-to-day issues of real clinical experience must still be accomplished.

In the past, undergraduates were too often left in the dark about what would be expected of them, when they are called upon to deliver health services in private practice and in the wider sphere of public service. Fortunately, this situation is rapidly being changed by the creation of departments of community health in many medical schools throughout the country. These efforts should be openly acknowledged and encouraged. The reason is simple enough: while it is important that the results of research be taught, it is equally important that students know how to put these facts to widespread clinical use among all the patients in need of them.

Teaching students how to keep up to date with the facts after graduation, and how to apply these facts in

future medical practice, are two criteria by which to measure the relevance of medical education. But relevance to what? The same answer is given in different ways by all the participants in this Forum. To be relevant, medical education must also actively work toward giving students an understanding of the *socio-economic and humanistic* determinants of health—which if ignored, can make purely clinical accomplishments barren indeed.

Preparing students for tomorrow's medicine in these three areas, I believe, should not be postponed in anticipation of hoped for attendance at continuing education programs later in life. Participation in these programs is most difficult when physicians are building and maintaining busy practices at inconvenient distances from major postgraduate centers. Rather, it is while *still undergraduates* that students should be convinced that their undergraduate studies are merely a short prelude to essential life-long learning in their profession. In fact, perhaps 75 percent or more of their medical education is yet to come.

To deal with this situation, undergraduate curricula should incorporate elements of *continuing re-education to change*. In the first instance, this means making extensive use of pedagogical techniques that will help to establish patterns of learning that can be sustained during the early and later years of medical practice. For example, radio, television, and other educational modes should be widely used as part of our undergraduate training, in addition to didactic lectures and personal discussion. The use of these techniques during the undergraduate years would surely facilitate their acceptance as vehicles for post-graduate education in later professional life. Further, students could attend graduate programs in continuing medical education together with practicing physicians—both at major medical centers and at community hospitals. Other specific approaches could also be suggested. The main point is that by *early exposure to postgraduate education, the framework for continuing re-education can be established for an entire professional career.*

However, this pattern should not be employed exclusively for the acquisition of the latest scientific information. That would merely be preparation for technical refurbishing. Tomorrow's physician must also be made amenable to the needs of multi-dimensional man in an increasingly complex society. To do this, undergraduate curricula should include an increasing amount of time for specific training in the broad gauged problems affecting both participants in the process of health care—the physician as well as the patient. This could be accomplished, for example, by undergraduate participation in private practices or public health agencies; perhaps, with supervision, they could be formally encouraged to initiate and service community health programs of their own.

But over and above preparing for future proficiency in purely technical matters, I believe it is necessary that the sharp edges of science be rounded off. Without early cultivation of humane insight into the ethical and philosophical basis of medicine, intellectual resiliency and human understanding cannot be maintained. And without this, the science of medicine may become deficient for its lack of art. Therefore, in addition to technical courses and practical training, undergraduate education should also include *courses in the humanities*, and perhaps participation (together with practicing physicians) in multi-disciplinary symposia on the humanities, health, and society. Such symposia could, and should, be given in local communities as well as at major teaching centers.

The content of medical education has been drastically altered by the sustained pressures of social and technological change. But if the potential benefits of technical advances are to have widespread clinical fruition, an educational pattern for the future should be laid early. I believe we can all agree that this pattern should aim at something more than maintaining technical proficiency. A relevant medical education should prepare students to cope with the total health needs of patients in a changing society whose problems we must inevitably face. It is best that we begin our preparations now.



### Differentiation of Extrahepatic And Intrahepatic Obstructive Jaundice

THE DIFFERENTIATION between extrahepatic and intrahepatic obstructive jaundice is readily made in 85 to 95 percent of cases. In the remaining 5 to 15 percent accurate diagnosis cannot be made on the usual criteria, and careful evaluation, including history, physical findings, biochemical and radiologic procedures, does not lead to a definitive diagnosis. It is in this group that oral and intravenous cholecystography rarely helps due to inability to adequately visualize the gall bladder and the common duct under these circumstances.

Fourteen years ago an international symposium entitled "Hepatitis Frontiers" (October 1956) was held at Henry Ford Hospital in Detroit. Dr. Henry Bockus put this question to the panel: "You are caring for a jaundiced patient. At the end of three weeks all tests remain inconclusive but leaning toward obstruction. What do you do next?" Need I say that six internationally recognized figures in liver disease who were present gave six different nondefinitive answers? Since complications of surgical operation and the attendant anesthesia are both frequent and severe in the presence of hepatocellular disease, it is extremely important that abdominal exploration not be undertaken in these situations. On the other hand, undue delay in the presence of extrahepatic obstructive jaundice may lead to irreversible secondary liver damage. The UCLA Interdepartmental Conference appearing in this issue is, therefore, particularly appropriate and timely.

I would emphasize that an adequate and thorough history and physical examination continue to be the cornerstone for accurate diagnosis in the vast majority of cases. Biochemical liver function

tests taken in relation to each other can be extremely helpful. Unfortunately no single biochemical function test will accurately differentiate in all situations. As with cholangiography, the biochemical tests are least helpful in those situations where help is most urgently needed. The percent conjugation of bilirubin, level of alkaline phosphatase, and cholesterol, level of serum enzymes and ratios of these enzymes, etc., may be misleading. Where evidence is inconclusive the clinician is faced with the following possibilities for further evaluation: (1) peritoneoscopy; (2) liver biopsy (transcutaneous); (3) cholangiography (oral, intravenous, and transcutaneous). More recently "selective" and so-called "super-selective" angiography, hepatic and pancreatic scanning, and transjugal, transhepatic cholangiography have all become available. The first two are undoubtedly more widely used at present than is the latter.

Although peritoneoscopy avoids the dangers of a general anesthetic it requires a person experienced and expert in interpretation. Where such a person is available this procedure may often be very helpful. Both percutaneous biopsy and trans-thoracic cholangiography may be helpful, but in the presence of extrahepatic obstruction they carry a significant element of risk. This risk must be equated with the risk of exploration and general anesthesia in each case. Inflexible guidelines cannot be established. Of the three procedures discussed in the previously mentioned UCLA Interdepartmental Conference, selective angiography has been by far the most commonly used. It has been proved to be helpful in a significant number of cases. Hepatic and pancreatic screening on the other hand are still in the developmental stage and interpretations of liver and pancreatic patterns are difficult and may be misleading. Perhaps the most exciting and promising is the method of transjugal, transhepatic cholangiography discussed by Dr. Martin Pops in the UCLA Conference. It is apparent, however, that secondary infections and



significant Gram-negative bacteremias can occur following this procedure. Certainly more extensive experience will be needed before the safety of this procedure can be accurately determined. Finally, the increasing awareness of the role of Australian antigen makes this test of possible potential help in differentiating between extrahepatic obstruction and the intrahepatic obstructive type of viral hepatitis. As biochemical parenchymal cell liver tests become more precise, it is to be expected that precision of differentiation will increase. However, in view of varying degrees of parenchymal cell damage at various stages of extrahepatic obstruction, it appears unrealistic to expect that any single biochemical test will, in all cases, accurately differentiate for the clinician. Accurate diagnosis continues to rest on a thorough history accompanied by careful evaluation of physical findings and biochemical testing. Wise selection by the physician of the specialized techniques mentioned in this issue will help to establish the definitive diagnosis in virtually all cases and avoid needless celiotomy.

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## World Medicine and the Coming Millennium

IN ANOTHER 30 years humanity will have reached A.D. 2000 and just one more generation of humans will have made whatever is to be its contribution. But this is not to be an ordinary 30 years. The next three decades will be as crucial for the ultimate health, well-being and survival of the human species as any, if not all, that have gone before. Standing upon what appears at once to be the threshold of unprecedented opportunity and the brink of utter disaster, we find ourselves curiously uninformed and unprepared, and in fact only just beginning to be a little bit concerned.

The major ingredients of this impending crisis are well known. The numbers of humans are being

increased with quite reckless abandon. The new capabilities of science, technology and industry are not only to release humans from labor and ignorance and to extend life, but also to consume resources and to pollute and distort the natural environment with very little regard for the consequences. The fact is that there has been too little attention paid to the natural characteristics of humans or to the harsh reality that what have always been considered endless land, sea, air and other resources are both finite in amount and fragile in quality.

It seems reasonable to predict that in the 1970s there will be much talk of ecology but that the talk will considerably outdistance significant action, simply because there is too little knowledge of what to do and too little experience with how to do it. In the 1980s the need to industrialize backward nations to support their growing population will surely be overpowering and will severely strain world resources of all kinds. And by the 1990s this industrialization and rising expectations will likely bring about a demand the world over for access to health and well-being similar to that which is now being pressed in this nation. A great danger is that the social, economic and political responses will, as now, be too hastily considered measures to meet a succession of crises and that by the millennium, A.D. 2000, the cumulative ecological crisis may have reached proportions such as seriously to threaten not only health but even survival for humanity on this planet.

We enter these crucial times with too many of our human institutions ill-adapted, confused or hopelessly bogged down by rules and traditions designed for other times and needs. Our leaders, liberal and conservative alike, are more concerned with imposing their conceptions of what they think ought to be, than they are with the real what is. The social sciences, those disciplines which should be primarily concerned with the realities of human nature and human behavior, have instead been largely preoccupied with attempts to design systems based on some theoretical concept of how things ought to be, rather than on how they are. By and large the professions have been backing away from their special responsibilities to an increasingly technologic and interdependent world society. In a kind of desperation this nation now seems actually to have turned to the consumer, crowned him king, and begun to wait patiently in the full expectation that somehow his native wis-

dom and accumulated experience will find the way where others have failed.

The new generation senses some of what is wrong but quite understandably it lacks the sophistication to deal with it. Among them the realization is dawning that life on this planet has become an entirely new game. Man is pressing his economic and environmental resources to their limits and sometimes beyond, and in turn these forces are beginning to close in upon humanity. Full recognition that the rules of this new game are the harsh rules of a closed biological system, and nothing else, has yet to arrive. But whether this is recognized or not, the moves made in this new game are increasingly likely to be for keeps. Also not yet fully recognized is the fact that these moves must be made within the framework of human nature and human behavior and that there must develop some world-wide coordination of the actions to be taken.

There is one profession, and only one, with the knowledge of human nature in health and disease and with the experience in human biology which will be needed, which can speak with the kind of authority which will be required, and within which there exists a dedication of purpose and channels of communication which transcend political boundaries. Medicine is this profession.

It is suggested that the World Medical Association be now called upon to assume leadership for the profession, and to conduct a responsible and continuing effort to guide the massive effort which will soon be needed if health, well-being and even survival are to be achieved and maintained in this closed and biological earth eco-system from which there can be no practical escape. Else the millennium may be too late.

## Progress in the Treatment Of Heart Disease

DISEASE OF THE HEART and blood vessels is responsible for approximately one million deaths each year in the United States and accounts for the majority (55 percent) of all deaths among

Americans. These alarming observations emphasize that the leading health problem facing our country continues to be mortality and morbidity due to heart disease. Yet considerable progress has been achieved in the past two decades both in the understanding of cardiovascular disorders and in the delivery of these advances to the people in improved care—thereby demonstrating that health research enhances rather than competes with health care. The death rate has been reduced in acute myocardial infarction, the incidence of rheumatic heart disease has been decreased, survival in congenital heart disease has been increased, and longevity in severe hypertension has been extended. These favorable developments, which perhaps have been more dramatic in cardiovascular diseases than in any of the other disciplines, are attributable to the enlarged programs of research, education and community service supported by public, private and professional interests working together to improve prevention, diagnosis, management and rehabilitation.

In recognition of the desirability of integrated discussion between investigators and clinicians, the postgraduate symposium, "Recent Advances in Cardiovascular Therapy," was presented by the American College of Cardiology and UCD School of Medicine on January 14 and 15, 1969. It is appropriate that the two papers selected from that conference for publication in this issue represent different aspects and approaches and thereby serve to underscore the broad scope of therapeutic accomplishments in heart and related diseases.

The most significant advance in cardiovascular medicine and research in the past 25 years appears to have been the development of methods for the catheterization of the human heart which can be carried out with ease and safety. Beginning in the 1940s with the groups at the Columbia-Bellevue, Peter Bent Brigham, and Johns Hopkins hospitals, application and refinement of these techniques have allowed new appreciation of pathophysiologic mechanisms in heart disease and have established cardiovascular diagnosis and evaluation on a scientific basis. The ability to define precisely and to quantify even the most complex cardiac disorders has spearheaded innovations in medical therapy, successful surgical treatment, and investigative interest in heart disease in general.

Truly remarkable progress has been achieved in surgical operations on the human heart since the first successful intracardiac procedure, a mitral



commissurotomy performed by Bailey in 1950. Cardiovascular surgeons have maintained close pace with the diagnostic sophistication of their medical colleagues. Outstanding examples are the evolution of open-heart surgery affording direct visualization within the heart for prolonged periods by use of the pump-oxygenator for cardiopulmonary bypass devised and applied clinically by Gibbon in 1954 and the development of an effective prosthetic cardiac valve by Harken and Starr in 1960. A large number of procedures have been conceived which clearly have decreased morbidity and mortality in congenital and rheumatic heart disease. Exemplifying these favorable results are the extraordinary advances in the correction and ingenious palliation of virtually all of the various congenital anomalies, as reviewed by Gerbode and Sharma elsewhere in these pages. In addition, the recent development of coronary jump-graft techniques by Favaloro and Effler appears to promise the potential extension of this therapeutic horizon to patients with coronary artery disease as well. Although several major problems remain to be solved, the most dramatic definitive therapy of established heart disease available at this time consists of surgical intervention. It is incumbent upon those of us who evaluate patients with cardiovascular disease to identify and select patients who may be expected to benefit from these procedures.

The principal problem in cardiovascular medicine today is coronary artery disease and the primary emphasis of the American Heart Association is now proclaimed to be the prevention of atherosclerosis. While the attainment of this goal appears long-term, new information has contributed considerably to our ability to recognize certain "coronary-prone" persons. Although predisposition to coronary artery disease in the presence of abnormal plasma concentrations of cholesterol and triglycerides has been appreciated for some time, the recent development of plasma lipoprotein phenotyping by Fredrickson, Levy, and Lees has contributed prominently to systematic classification with implications for management of lipid disorders. In patients with accelerated coronary artery disease (symptoms before age 50) as many as 80 percent have lipoprotein abnormalities. Simplified classification and current knowledge of the hyperlipoproteinemias are considered by Zelis and co-workers to provide a therapeutic approach and identification of affected family members. This

report contains preliminary data of the first objective evidence of regression of ischemic vascular disease, in patients with Type III or "broad beta" disease following therapy with diet and clofibrate (Atromid-S®). These workers also have recently shown that clofibrate is capable of lowering elevated triglycerides in Type IV patients even when rigorous dietary control cannot be achieved. In atheromas associated with the most common abnormalities (Type II and IV) the lipids may not be labile and, indeed, regression of coronary lesions has not been observed despite prolonged control of plasma cholesterol achieved by ileal bypass. From these observations, the value of maintaining plasma lipids within normal levels at present appears directed at prevention and reduction of progression of plaques rather than resolution of existing atheromas.

Since the fruits of effective preventive measures in atherosclerosis are not likely to be realized for several years, one of the major practical concerns at present is early recognition of potential victims of sudden death, since 60 percent of mortality from acute coronary episodes occurs outside the hospital. As to patients who do reach the hospital, the coronary care unit (CCU) has halved mortality in certain medical centers, from 30 percent to 15 percent. This great advance is the result of effective detection and management of arrhythmias and represents the potential of more than 50,000 lives saved each year in the United States. In acknowledgement of the remarkable success of the CCU concept in reducing mortality due to abnormalities of cardiac rhythm, considerable interest has developed in such matters as emergency pre-hospital transport systems, special training of paramedical personnel, improved care in the hospital emergency room, use of prophylactic anti-arrhythmic drugs, the value of early use of lidocaine and atropine, expanded application of cardiac pacemakers, and post-CCU units designed to reduce hospital mortality in the second and third week following infarction.

Efforts to overcome cardiac pump failure, however, have been quite unsatisfactory. This complication now accounts for the majority of deaths in the CCU and is fatal in more than four out of five patients in whom it occurs. Although understanding of this shock syndrome is incomplete, it appears that it is particularly related to the extent of the infarction and the response of the peripheral vasculature. With reduced cardiac output result-



ing from loss of myocardial contractile units, diminished inotropic state, and ventricular asynergy, it is postulated that shock develops when there is an inadequate rise in systemic arteriolar resistance. In contrast, with an appropriate increase in resistance sufficient to prevent hypotension, congestive heart failure is observed. Since pharmacologic therapy has not substantially improved mortality in cardiogenic shock, there is now considerable interest in mechanical means for supporting the circulation such as counterpulsation, partial and total circulatory bypass, and pump-assist devices. A unique approach which has been successful experimentally—and the efficacy of which is now being evaluated in our CCU—is retrograde perfusion of the coronary sinus with oxygenated blood at arterial pressure.

In the study of coronary disease, the indications for coronary arteriography are broadening. It is now our practice to employ this procedure for evaluation in refractory angina, in patients under 50 years of age with ischemic pain, and for definitive diagnosis in certain difficult problems of chest pain of undetermined cause. Since angina pectoris may be considered the clinical expression of a disparity between the requirements of the heart for oxygen and the availability of coronary blood flow, relief of ischemic pain can be achieved by diminishing the former or improving the latter. Consistent with this observation is that the extent of myocardial infarction is directly related to the demands of the heart for oxygen at the time of interruption of the coronary circulation and implies the potential value of propranolol in pre-infarction angina. Current evidence suggests that the salutary results of nitroglycerin, propranolol, weight reduction, exercise training, and carotid sinus nerve stimulation are principally based on reduction of myocardial oxygen consumption. Although the positive contractile action of digitalis increases myocardial oxygen needs, this agent can be useful in depressing angina when there is abnormal cardiac performance, which itself raises the oxygen requirements of the heart. It is rational to conclude that the frequency and intensity of angina might be improved by lowering the heart's oxygen demands by the prolonged action on the peripheral circulation of a vasodilator substance. Unfortunately, studies in our laboratories with long-acting nitrites have indicated the development of tolerance concerning venodilation with both their chronic effect and the acute action of nitroglycerin.

The only effective means at present available for substantially elevating blood flow to the ischemic myocardium appears to be the coronary bypass procedure in carefully selected patients. Medical means including antilipid measures and acute and chronic anticoagulation intended to enhance reduced coronary flow have not been successful. Experimental evidence now indicates that the genesis of arterial thromboses is the result of platelet aggregation and thereby is fundamentally different from the development of venous clots which are due to fibrin deposition. It appears that therapeutic measures such as operative myocardial revascularization techniques postulated to increase compromised blood flow through the development of collateral coronary circulation are largely ineffective. Consistent with this view is that exercise-induced ischemia, hemodynamic function, and even survival are not related to the extent of development of spontaneous collateral coronary vessels. Although collateral channels must be of a certain quantitative importance, they seem to represent a response to ischemia and impairment of the native circulation and their degree of development correlates only with the magnitude of coronary vessel disease itself.

In the treatment of refractory angina pectoris, the relative roles of coronary surgery and carotid sinus nerve stimulation are not settled. It is our current choice to employ vein grafts in suitable lesions, particularly those in young patients with localized disease and in whom rehabilitation is of special importance. The carotid sinus nerve stimulator is used in older patients with diffuse coronary involvement and in those who do not obtain relief following operation on the coronary arteries. We recently have extended the recommendation of coronary bypass procedures to patients, particularly those less than 50 years of age, with favorable lesions and disabling angina without requiring previous trial with propranolol. It is suspected, but not proved, that treatment with propranolol, although relieving ischemic pain, might not sufficiently improve survival in these patients. Further extension of the bypass technique to patients with advanced localized obstruction but less severe angina in an attempt to prevent infarction must await additional evaluation of operative results.

In the management of chronic refractory congestive heart failure due to coronary artery disease, operative resection of abnormally contracting ventricular segments has been documented to be of

considerable value in certain selected patients. In our experience, this evaluation is aided by the finding of dissociation of hemodynamic function from the mechanical properties of the ventricle. Also, asynchrony of contraction is an important component of depressed pump function and reduced cardiac output immediately following acute myocardial infarction. It is hypothesized that in some instances the ineffectiveness of certain positive inotropic agents in the treatment of cardiogenic shock might be the result of worsening of this disorderly sequence of ventricular contraction despite improvement of depressed contractility.

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## A Policy on Strikes

THE HOUSE OF DELEGATES of the California Medical Association has adopted a significant and timely statement with respect to strike activities by physicians. (The statement appears in full in the box opposite.) It declares that the CMA "believes that abandonment of patients through a concerted denial of service by physicians (strike) is an unacceptable method of solving problems or differences," and goes on to emphasize the importance of reason, reasonableness and cooperation in achieving desired objectives. The statement is significant because it reaffirms a time honored value system which places a physician's service to humanity somewhat above such things as hours of work, remuneration and fringe benefits, while at the same time holding that these should be fair and equitable. The statement is timely in that it calls for a return to reason and reasonableness at a moment when the use of power tactics in health

care is increasing and seems likely to increase considerably more.

The 1970s are certain to be a period of enormous pressures in health care. The root of the evil lies in the disparity between unrealistic expectations of health care services on the one hand and unrealistic assumptions with respect to resources for their delivery on the other. A situation exists which is poorly understood and which is impossible of immediate solution. In such circumstances there is a danger that irrationality will replace reason and that power tactics will be employed in certainly futile and potentially devastating efforts to overcome the real and imagined

### A Position on "Strike" Activities

A policy statement on the California Medical Association's position on "strike" activities was adopted by the House of Delegates at its meeting March 11, 1970. The statement follows:

"The physicians of California have one major responsibility and duty: the provision of medical care of the highest quality to all persons. The California Medical Association believes that abandonment of patients through a concerted denial of service by physicians (strike) is an unacceptable method of solving problems or differences.

"The California Medical Association further believes all members of the health team should receive reasonable and fair compensation, benefits and privileges for their services. These rewards would be based, primarily, on education and training, experience, responsibilities and competence.

"The California Medical Association urges that methods be sought by all members of the health team, including those administrative and political agencies which use the services of health workers, to achieve their desired objectives in an equitable, professional manner, protective of the health of all, without resorting to denial of service.

"The California Medical Association will continue to cooperate with the hospitals of California and with professional organizations representing members of the health care team, for the purpose of improving the quality and increasing the availability of health manpower personnel through (a) improving recruitment techniques; (b) providing more educational and training opportunities; and (c) urging adequate compensation of personnel in terms of their education, experience, and degree of responsibility and competence in health care."

injustices inherent in the impossible situation. It makes no difference whether the power tactics are used by government, by third party payers or by health professionals. The ultimate result of their use is always reduction in efficiency and an increase in the real cost of delivering health care services. Seldom is the patient's or public's interest served by such tactics, and where reason prevails they should not be necessary.

In retrospect many would say that the government was irrational when it decided to pour billions of dollars into providing payments for additional health care services without making parallel provision for the additional resources needed. It has been frustrating to those within and without government to find the cost of these services has risen although reason tells us there could have been no other result. To try to control the rising health care costs, further irrational acts by government and others are clearly impending, and these will no doubt further reduce efficiency and further curtail what few incentives remain for a physician to expand his services. The inevitable result will be further to increase the real cost of the services rendered and also the disparity between expectations and resources which is after all the root cause of the problem. Power tactics, whether used by government, nurses, interns and residents or others are as irrational in health care as indeed they are elsewhere in human relations where the common

good, and perhaps even the survival, of all is at stake.

The CMA action might well have been to climb on this power bandwagon. But it was not. Instead the statement of the House calls for the greater use of reason and statesmanship. It places the health and health care of patients and the public a notch or two above the battlefield of power tactics and power politics in health care. It recognizes the frustrations, the problems and the differences but holds that these can be better resolved with reason and reasonableness than with force in the interest of the common good. This is a challenge not only to physicians, nurses and other health professionals but to society itself and its government.

Were the alternative philosophy to prevail, or indeed to come about at some future time, and if doctors were really to decide to hang together and to hang tough enough, one suspects they could get just about anything they wanted from government and the public. But this is not the present attitude of the great majority of the House of Delegates or of practicing physicians, and it is in the interest of all concerned that the statement of the House be commended and supported. If reason can become the order of the day, it will in the long run result in better and less costly medical care and a fair shake for everyone including all the health professionals. The House is to be commended for so rational and forthright a stand.



## Information

### Treatment of Hypertension

HARRIET P. DUSTAN, M.D.

*Material Supplied by the American Heart Association*

**HYPERTENSION SHORTENS LIFE.** Even the so-called benign hypertension causes premature death or disability and can scarcely be looked upon as benign. Considering that hypertension is potentially lethal, the question arises as to whether sustained reduction of arterial pressure prolongs life. There are two answers to this question: an unqualified "yes" and a "maybe," depending on whether reference is made to the complications of arteriolar disease or those of atherosclerosis. The most frequent results of hypertensive vascular disease—the term used for the arteriolar disease—are cardiac failure and malignant hypertension. In both instances blood pressure reduction is life-saving providing, of course, that in the malignant hypertensive renal function is still adequate to sustain life. Clinical experience also indicates that good blood pressure control in hypertensive patients without these complications will prevent their occurrence. In contrast, the effects of antihypertensive treatment on the complications of atherosclerosis are not so clear as on those of hypertensive vascular disease, and here the "maybe" answer has to be given. The equivocation in this answer comes because antihypertensive drug treatment has not been used over a long enough period of time to assess its effects on the complications of atherosclerosis that so frequently accompany hypertension. However, there is some evidence which suggests that strokes, at least, occur less frequently in treated patients.

From the foregoing, the goals of antihypertensive treatment can be stated as: (1) to reduce arterial pressure to normal or as near normal as possible, (2) to prevent the progression of arteriolar disease and control its complications if they are present, and (3) to prevent the development of premature atherosclerosis—or at least to prevent or postpone the development of its complications.

There are a variety of ways to treat hypertension effectively. Some are specific in that they eliminate or block a pressor mechanism and thus reduce arterial pressure to normal. Others can be called non-specific because, although hypertension is greatly lessened, arterial pressure does not become normal. The treatments which in my opinion are specific are both surgical and medical. In a young patient with renal arterial stenosis, a successful operation—either a revascularization procedure or nephrectomy—usually completely eliminates the hypertension. In a substantial number of patients with pheochromocytoma, primary aldosteronism and coarctation of the aorta similar results are achieved by operative treatment. Certain drug treatments also achieve complete normalization of arterial pressure. Thus, in patients with primary aldosteronism, administration of spironolactone eliminates hypertension as surely as does operative removal of the tumor; and in patients with increased activity of the beta-adrenergic component of the sympathetic nervous system, use of a beta-blocking drug such as propranolol not only abolishes the symptoms but also reduces arterial pressure to completely normal levels.

The experience with these "specific" treatments is striking because such results are usually not achieved when the pressor mechanism is not approached directly. For example, contrast the blood pressure reduction achievable by successful operative treatment in a patient with renovascular hypertension with the result produced in the same patient by a drug, like alpha methyl dopa, that suppresses sympathetic vasomotor activity. In the former instance, the operation eliminates the pressor factor(s), while in the latter drug treatment lessens the hypertension but does not eliminate it. The operative treatment is specific, while the drug treatment is nonspecific or empiric.

The fact that most drug treatment of hypertension is empiric is not to say that it is unsuccessful, because substantial reductions in arterial pressure can usually be achieved. There are a number of drugs available which are effective and,

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for the most part, reasonably easy to take. Two types are most commonly used—oral diuretics and drugs that suppress the activity of the sympathetic nervous system through effects on production, storage or release of the neurotransmitter, norepinephrine. The former group includes chlorothiazide and its derivatives, as well as ethacrynic acid and triamterene; the latter comprise ganglion-blocking drugs, reserpine, guanethidine, alpha methyl dopa and pargyline. Not included in these two groups is hydralazine, which seems to act directly on the arterial wall. The anti-aldosterone drug, spironolactone, has value as nonspecific treatment when used to combat the potassium losing effects of chlorothiazide diuretics.

When used in adequate doses, these drugs usually achieve good blood pressure control. When more than one drug is used, combination tablets are not the best way to administer the medication because there is need to individualize the dose of each drug. The most frequent combination of drugs is an oral diuretic with another type because usually there is a synergistic effect on blood pressure reduction—the combination achieving a better result than would be expected from purely additive effects of the two drugs. Not more than one type of chlorothiazide diuretic should be given in a treatment regimen, and, also, there is no evidence that giving more than one type of adrenergic-blocking drug—such as combining guanethidine with methyl dopa—adds any benefit.

When it is necessary to reduce blood pressure rapidly, as in patients with cardiac failure, intracerebral bleeding or hypertensive encephalopathy, good results can usually be achieved by the potent peripherally-acting sodium nitroprusside or diazoxide given intravenously. More readily available, but less potent, are preparations of reserpine,

hydralazine, methyl dopa, and ganglion-blocking drugs suitable for parenteral administration.

One crucial question in the long-term treatment of hypertension concerns how to judge the effect of treatment. Actually, use of office pressure measurements is usually unsatisfactory, but for certain patients there is no other way. However, many patients can learn to make their own measurements, and this provides a daily record of responses and allows for judicious adjustment of doses whenever indicated. One mistake that many clinicians make is failure to obtain a good pre-treatment arterial pressure record, and this difficulty can be obviated by use of home readings. The technique is easy to learn, and the measurement is no more difficult to carry out than estimation of urinary sugar—information considered a must in the treatment of diabetes.

With home readings, the physician has the advantage of judging the effects of treatment in two situations rather than one because he additionally obtains office readings when the patient visits him. The more detailed record of treatment response that is available the better can the treatment be managed.

In some patients with hypertension of unknown cause, use of nonspecific drug treatments detailed above reduces arterial pressure to normal just as specific treatments do in patients with known types of hypertension. Such responses show that each type of treatment can be specific when properly chosen; the current problem is that, for the most part, there is no sure way to make the proper choice. Currently, the challenge of investigation is to learn enough about the mechanisms of hypertension and how they are interrelated so that specific, rather than empiric, treatments can be given to each hypertensive patient.

### SUBACUTE BACTERIAL ENDOCARDITIS

"In 95 percent of all patients with subacute bacterial endocarditis, the causative organisms (most commonly *Streptococcus viridans*) are engrafted upon either a congenital or an acquired lesion. Therefore you have a murmur to start with. I have never seen a proved case of subacute bacterial endocarditis without a murmur. . . . It's the first important diagnostic sign."

—WESLEY W. SPINK, M.D., Minneapolis  
Extracted from *Audio-Digest Internal Medicine*, Vol. 16, No. 8, in the Audio-Digest Foundation's subscription series of tape-recorded programs.

# Medicine's Place in Aviation Safety

C. I. BARRON, M.D., *Los Angeles*

ONE HUNDRED PHYSICIANS, biomedical specialists, pilots, stewardesses, airport managers, Federal Aviation Administration representatives, crash and rescue personnel, and disaster planning personnel attended the second conference on Medicine and Air Safety in Los Angeles, January 30-31. The meeting, sponsored by the California Medical Association Committee on Disaster Medical Care, featured nationally recognized authorities from the aerospace community and covered topics varying from human capabilities and limitations to airport medical services and disaster planning. The following facts and conclusions evolved from the presentations and discussions generated by them:

- Despite our extensive knowledge of flight physiology, accidents due to inadequate pilot indoctrination and understanding still occur.

- Psychiatric evaluation for flying appears to be inadequate. Irrational acts by pilots still contribute to accidents.

- Present training procedures make it impossible to adequately prepare the student pilot for safe and proficient flying.

- While drugs are rarely incriminated in general aviation accidents, alcohol is a significant factor in flight safety and contributes to at least 15 to 20 percent of all general aviation accidents.

- Pilot factors account for over 80 percent of the almost 6,000 general aviation accidents occurring each year which result in over 1,000 fatalities.

- A systems approach is needed to assure that information gained in accident investigation is properly utilized in preventing accidents of similar type.

- Increasing emphasis is being given to assure the physical and emotional health of air traffic controllers, whose role in air safety is becoming increasingly important with the expansion in air travel and traffic.

- Stewardesses and cabin attendants are assuming increasingly important roles in the in-flight handling of passenger medical emergencies and in the emergency evacuation of aircraft. Their training in these fields is being increased to assure proper execution of these functions.

- With use of the jumbo jets, which are expected to provide a degree of comfort and safety unexcelled in aviation to date, a broad passenger mix is anticipated—an increased number of older, younger, and medically marginal passengers. The possibility of in-flight medical emergencies is thus increased.

- The continued growth and success of the Airport Medical Services Center at Kennedy International Airport demonstrate that private enterprise can operate an efficient and profitable airport medical service and that such a service can be most effectively integrated into the disaster emergency planning of the airport.

- The need for a coordinated emergency disaster plan for all major airports was stressed. This

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should involve all crash and rescue facilities, local police, medical resources, area hospitals, and communication media in the community. The need for proper communications, sorting and rapid evacuation of casualties, hospital disposition, and availability of skilled medical assistance is self-evident. Few such integrated plans exist today.

- Since many, if not most, fatal aircraft accidents occur off airport property, coordination of the airport disaster plan with the local community disaster plan is needed.

- A recent survey by the Airline Pilots Association has shown that only 110 United States airports have good fire crash rescue capabilities; whereas 197 have no capable equipment located on the air field.

- The county medical association is the logical agency to write the medical portion of the disaster coverage plan, fitting it into the general community disaster plan.

- There are currently no FAA regulations requiring certification of airports with respect to emergency disaster plans and facilities. Such regulations may be needed if local authorities are unable or unwilling to provide adequate plans of their own.

- The air evacuation helicopter offers great promise for rapid evacuation of aircraft accident casualties; however, its capacity may be inadequate in accidents involving mass casualties.

- A good emergency plan should include all available rescue agencies and resources, including

those from nearby military bases, Coast Guard and civilian sources.

- At the end of the meeting, a resolution was passed requesting the Council of the California Medical Association to introduce a resolution before the CMA House of Delegates requiring that (1) the CMA assume a role of leadership by assembling the proper private and government organizations to further pursue this matter; and (2) that an Interagency Council with representation from the appropriate organizations be formed to implement the recommendations from these conferences, and (3) that each component medical society should assess its own requirements in light of any possible disaster and prepare plans to suit the individual needs, including assistance in coordinating their efforts with nearby facilities and organizations. The House adopted the resolution.

In summation, it appears that much is known about man's capabilities and limitations and of the stresses produced by the aerospace environment in which he flies. Despite this, accidents still occur for the same reasons as in the past, and many of these result from pilot-induced factors. It appears that the major problem in aviation safety is the application of our existing knowledge to aircraft accident prevention training, with increased emphasis on pilot indoctrination. It also appears that a more vigorous effort on the part of the local communities working with responsible airport authorities and organized medicine is needed in order to assure optimization of airport emergency plans.

### BACITRACIN-RESISTANT STAPHYLOCOCCI

"In the past we have advocated the use of bacitracin in the therapy of serious staphylococcal disease in newborns. But in recent months under widespread monitoring, we have found bacitracin-resistant staphylococci have appeared all over the United States in a rather explosive fashion. They've been behind schedule; they should have appeared about a decade ago. But they are just beginning to appear now and they are rapidly increasing. For this reason, we no longer advocate the use of bacitracin on severe staphylococcal disease."

—HEINZ F. EICHENWALD, M.D., Dallas  
Extracted from *Audio-Digest Pediatrics*, Vol. 15, No. 4, in the Audio-Digest Foundation's subscription series of tape-recorded programs.

# LETTERS *to the Editor*

## The Myths and the Words

*To the Editor:* I cannot refrain from commenting on the editorial in CALIFORNIA MEDICINE, March, 1970, entitled "Costly Mythology in Health Care." Just as myths tend to persist and dominate our thinking, so also are we often victims of words and the definitions applied to them by various people. I think we are in such a situation in terms of the words "health" and "health care" and "medicine" and "medical care." I think much of the impact of the editorial was lost in the confusion—or rather the implication—that health care services and medical care services are the same.

I think we must accept the fact that nutrition, housing, education, economic status and the like are variations in health care services, and that we should separate from these, those things that are considered medical care services. Thus, if one accepts as the editorial writer did, a broad definition for health, then everything contributing to it must be considered a portion of the health care delivery system. It is quite true that it is a myth to believe that scientific medicine alone can automatically guarantee good health.

It is apparent, I think, to all that medical care is one component albeit a very important component of the larger health care system. Many of the problems now facing us, many of the criticisms leveled at the medical care system, should be focused in those areas which can actually do some-

thing to alter and solve the problem if we would only accept the fact that health is more than just the delivery of medical care. Health is the end result of many factors in the social structure that relates to and from an individual.

We, in medicine, have enormous problems in improving the medical care system, but it is a crushing and destructive load on that system to place all aspects of health within it. The medical care system may well serve to detect the need for changes in social structure in order to promote greater health, but I do not think the medical care system can be the actual change agent, but rather that body which brings these needs to the attention of other social groups.

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## A Word About "Epitomes"

*To the Editor:* Congratulations on your new section, "Important Advances in Clinical Medicine." Most of the brief statements in the February issue proved very good indeed. Somewhat too brief, I felt, were the two statements by Dr. William M. Todd on "Suppression of Rh Sensitization" and "Amniocentesis." I also should like to take exception to one statement made by Dr. Garson H. Tishkoff in his paragraph on "Treatment of Hemophilia with Newer Blood Factors." He states: "fresh frozen plasma remains the agent of choice in the control of minor bleeding and hem-

arthrosis." I disagree most heartily. I have used no fresh frozen plasma in the treatment of classical hemophilia since cryoprecipitates first became available. Adequate treatment with cryoprecipitates in most areas is less expensive than the usually inadequate treatment with fresh frozen plasma.<sup>1</sup>

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School of Medicine*

1. Hattersley PG: The treatment of classical hemophilia with cryoprecipitates — Laboratory control with readily available tests. *JAMA* 198:243-247, 1966

## Relevance in Medical Education

*To the Editor:* The relevance of medical education is almost totally the responsibility of medical educators and during the past ten years I have had

great doubts as to their sensitivity to their responsibilities. It does not take long to find out that medical school graduates realize that their medical education has prepared them to serve a system for delivery of health care which no longer exists and yet medical educators continue to produce this antiquated product.

I grant that medical educators have a difficult task, since the ultimate new form of the delivery of health care in our country and the world is not yet discernible, and they are therefore forced to redesign curriculum without a clear knowledge of the system which the curriculum must serve. It seems to me, however, that one change is obviously needed. Medical schools must no longer continue to be narrowly dedicated to producing products to fit a system over which they have no control. Medical educators must bear part of the burden of finding solutions to our nation and world's health problems and this means involvement in experimentation with new systems and in the political and sociological aspects of health care.

GLEN G. CAYLER, M.D.

*Sacramento*

## ANESTHESIA FOR CESAREAN SECTION

"It's true that I have ways of giving general anesthetics to mothers without causing much depression of their babies; but I can't guarantee it. I am reasonably sure, but not absolutely. So if I want to give a general anesthetic to a mother and have minimal effect on the child, the technique that I now use, that I try to get my department to use, and that I try to get our obstetricians to accept, is this: You put the mother to sleep with a dose of pentothal adequate to produce unconsciousness; you then let her breathe 50 percent oxygen; you start an intravenous drip of a paralyzing drug that runs in and paralyzes the mother completely so that she cannot twitch a muscle—absolutely no movement whatsoever. The operation then starts and the obstetrician gets the baby out as fast as he can. Babies born in this way have no perceptible depression that I can make out because the paralyzing drug does not cross the placenta. The amount of pentothal and nitrous oxide in the mother is not very great, and I believe that you can get perfectly good babies in this way. As a matter of fact, it is my method of choice. If any of you were to ask me to take care of a patient of yours for a cesarean section and I were faced with the need to give a spinal or an epidural or this technique, I would use this technique."

—JAY J. JACOBY, M.D., Philadelphia

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## Dr. Lloyd H. Smith, Jr., Named To President's Science Advisory Committee

LLOYD HOLLINGSWORTH SMITH, JR., M.D., has been appointed by President Nixon to the President's Science Advisory Committee for a four-year term.

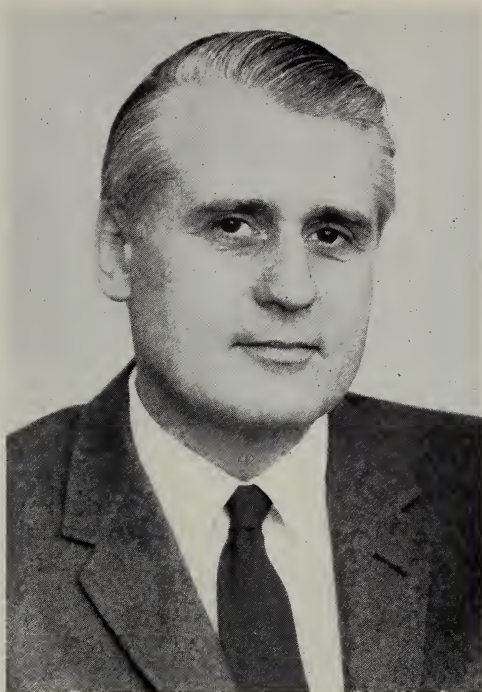
Dr. Smith, who is associate editor of *CALIFORNIA MEDICINE*, is chairman of the Department of Medicine at the University of California, San Francisco, and is professor of medicine and physician-in-chief of the medical staff. He is president of the American Society for Clinical Investigation; president, Western Society for Clinical Research, and a member of a number of editorial boards.

The new appointee to the Science Advisory Committee was graduated in 1944 from Washington and Lee University, where in 1969 he was awarded an honorary Doctor of Science degree. He received his doctorate in medicine from Harvard Medical School in 1948.

Further training was taken at Massachusetts General Hospital where later he served as chief resident in medicine, assistant in medicine, and assistant professor of medicine at Harvard Medical School.

He also served as visiting investigator at Oxford University's Department of Biochemistry in England, and at The Karolinska Institute, Stockholm. In 1964 he came to the University of California as professor of medicine and chairman of the department.

The functions of the Science Advisory Committee on which Dr. Smith will serve until December 31, 1973, are, as set forth in November 1957, "to make scientific advice and analyses available when needed in the formulation of national policy." The committee recently has sought to further their objectives "to insure that science and technology contribute their maximum to the defense of the U.S. and the free world; to extend the recognition of science as a creative activity that augments man's dignity and understanding and affords him intellectual adventure of the highest order; to recognize that outstanding accomplish-



LLOYD H. SMITH, JR., M.D.

ments in science appeal deeply to the hopes and aspirations of men everywhere and contribute to the prestige and good will of nations; to apply it more effectively to improve the health and welfare of people; to improve communications between government and civilian scientific efforts; and to promote international understanding and good will."

Established under the Eisenhower Administration, the committee consists of 16 to 18 scientists of varied backgrounds, including one behavioral scientist. Chairman is Dr. Lee A. DuBridge, former president of the California Institute of Technology. Members from California include Dr. Sidney Drell, Stanford Linear Accelerator Center; Dr. Murray Gell-Mann, professor of theoretical physics, California Institute of Technology, and Dr. Charles H. Townes, Department of Physics, U.C. Berkeley.

With this recent appointment, Dr. Smith will be attending meetings in Washington, where his immediate concerns will be medical research and health care needs.

# **Summary of Activities in California September 1968-August 1969**

THE CALIFORNIA MEDICAL ASSOCIATION'S Committee on Continuing Medical Education has completed its 1968-69 Summary of Continuing Medical Education Activities in California. This summary should be especially useful to sponsors offering continuing medical education as it lists geographically and by field of medical interest which activities have been recently available in California. Used as a basis for future program planning in conjunction with our "clearinghouse service," which will be described later, this summary can help avert unnecessary duplication and identify important areas left uncovered. However, educational efforts should meet the needs of the physician, and this consideration should be the paramount one in such decisions. Future articles will deal with approaches to discover such physician needs.

This summary includes all continuing medical education activities in California as reported to the Committee on Continuing Medical Education for the one-year period, September 1, 1968 through August 31, 1969. There were 620 activities representing 7,703 hours of instruction offered by 139 sponsors. Activities encompass meetings and courses and specialty society meetings at which scientific sessions were reported; and for the first time the 1968-69 summary includes formal radio and television courses and grand rounds. The number of activities and instructional hours are presented by geographical location, sponsorship and specialties and selected categories.

Table 1 shows the continuing medical education activities summarized by geographical location. The California Regional Medical Programs (CRMP) area designations reflect location only, and are not to be confused with sponsorship. Some 54 percent of activities were held in two areas of the state, Area I (30.8 percent) and Area IV

(23.9 percent). Eighty-seven percent of all activities were held in Areas I, III, IV, and V. Instructional hours tended to be somewhat greater on a per activity basis in Area V than in the case of the other areas, with Area V having 23.9 percent of all hours of instruction in the state, as compared with 19 percent of all activities held. While Areas II, III, VI, VII, and VIII contain 38 percent of California's physicians, these areas had only 26 percent of all activities and only 25 percent of all hours of instruction. The smaller areas of physician population tended to have fewer activities per physician, but the activities generally contained more hours of instruction. While nearly all California Regional Medical Program areas follow county lines, the one exception, the overlapping of CRMP Areas IV and V in Los Angeles County, makes the analysis of those areas difficult as the figures on numbers of physicians are available only on a per county basis. There is, of course, accessibility to educational activities in densely populated areas near bordering CRMP area lines, such as CRMP Areas IV and V.

Meetings and courses were the most frequent modality, accounting for 71 percent of the total number of continuing medical education activities and for 75 percent of all hours of instruction. Grand Rounds accounted for 5 percent of the total number of activities and for 23 percent of the total hours of instruction, while radio and television constituted 24 percent of all activities but only 2 percent of the total instructional hours. (See Table 2.)

As in 1967-68, medical schools were the most frequent sponsor, presenting 315 activities representing 3,756.5 hours of instruction and accounting for almost 51 percent of the total number of activities and 49 percent of all hours of instruction. In 1959-60 a total of 104 sponsors reported continuing medical education activities to the Committee on Continuing Medical Education; in 1968-69

Reprint requests to: CMA Committee on Continuing Medical Education, 693 Sutter Street, San Francisco, Ca. 94102.



	CRMP Area*	Activities		Hours		Number of Physicians In CRMP Area	
		No.	Pct.	No.	Pct.	No.	Pct.
TABLE 1.—Continuing Medical Education Activities—Summary by Geographical Location (September 1, 1968–August 31, 1969)	I	191	30.8	2,260	29.3	8,547	24.7
	II	25	4.0	332.5	4.3	1,908	5.5
	III	88	14.2	701.5	9.1	4,823	13.9
	IV	148	23.9	1,697	22.0	2,365	6.8†
	V	118	19.0	1,796.5	23.0	14,398	41.6†
	VI	13	2.1	264.5	3.4	1,728	5.0
	VII	22	3.5	448	5.8	2,782	8.0
	VIII	15	2.4	203	2.6	2,092	6.0
	Totals	620	100.0‡	7,703	100.0‡	38,643	100.0‡

\*CRMP designations reflect only the location where an activity was presented, and are not to be confused with sponsorship.

†Physician figures are compiled on the basis of county figures. CRMP Areas IV and V overlap in Los Angeles County, but this chart correlates CRMP Area V with Los Angeles County.

‡Percentages may not equal 100 because figures were rounded to the nearest tenth.

CRMP Area I: Del Norte, Siskiyou, Humboldt, Trinity, Shasta, Tehama, Glenn, Colusa, Mendocino, Lake, Sonoma, Napa, Marin, Contra Costa, Alameda, San Francisco.

CRMP Area II: Modoc, Lassen, Plumas, Butte, Sierra, Sutter, Yuba, Nevada, Placer, Yolo, Solano, Sacramento, El Dorado, Amador, Alpine.

CRMP Area III: San Joaquin, Calaveras, Tuolumne, Mariposa, Stanislaus, Merced, Santa Clara, San Mateo, Santa Cruz, San Benito, Monterey.

CRMP Area IV: Madera, Fresno, Kern, Kings, Tulare, San Luis Obispo, Santa Barbara, and part of Los Angeles, Ventura.

CRMP Area V: Major portion of Los Angeles County.

CRMP Area VI: Mono, Inyo, San Bernardino, Riverside.

CRMP Area VII: San Diego, Imperial.

CRMP Area VIII: Orange.

TABLE 2.—Continuing Medical Education Activities—Type of Presentation (September 1, 1968–August 31, 1969)

CRMP Area	Meetings and Courses				Grand Rounds				Radio and TV*			
	Activities		Hours		Activities		Hours		Activities		Hours	
	No.	Pct.	No.	Pct.	No.	Pct.	No.	Pct.	No.	Pct.	No.	Pct.
I	139	31.4	1,902.0	32.9	5	17.2	311	17.6	47	31.5	47	31.5
II	25	5.7	332.5	5.7	0	0	0	0	0	0	0	0
III	53	12.0	545.5	9.4	3	10.3	124	7.0	32	21.5	32	21.5
IV	66	14.9	861.0	14.9	12	41.4	766	43.3	70	47.0	70	47.0
V	114	25.8	1,506.5	26.0	4	13.8	290	16.4	0	0	0	0
VI	13	2.9	264.5	4.6	0	0	0	0	0	0	0	0
VII	19	4.3	274.0	4.7	3	10.3	174	9.8	0	0	0	0
VIII	13	2.9	99.0	1.7	2	6.8	104	5.9	0	0	0	0
Totals	442	100.0	5,785.0	100.0	29	100.0	1,769	100.0	49	100.0	49	100.0

\*Radio and television programs are included in the CRMP Area from which the broadcast emanated although coverage was over a larger area.

the total had risen to 139 sponsors. This 25 percent increase is mainly accounted for by an increase from 35 to 55 in the number of specialty societies reporting activities and from 8 to 21 of "other" sponsors, the category including California Regional Medical Programs, California Medical Association, county medical societies and research foundations. Where two or more organizations share sponsorship and responsibility for an activity, the primary sponsor is identified as the one that supplied program information. In some instances an activity was entirely planned by a medical school, but was sponsored by a specialty society or "other" sponsor. Likewise, medical school faculty are frequent participants in activities sponsored by groups other than medical schools (Tables 3 and 4).

The two medical schools presenting the largest number of activities, UCSF and UCLA, tended to have activities of shorter duration than those of USC and Stanford, which offered fewer activities.

The specialties in which the most continuing medical education activities were provided were Medicine (211 activities with 3,060.5 hours of instruction) followed by Surgery (106 activities with 1,272.5 hours of instruction). Five categories, Medicine, Surgery, Psychiatry, Pediatrics and General Practice, accounted for 80 percent of all activities and 85 percent of the total hours of instruction in the state. (Table 5.) It is of course possible for physicians to attend activities other than those in their specialty. It was noted in the summary's detailed report of surgical sub-specialties and selected categories [in a table included in the pub-



TABLE 3.—Continuing Medical Education—Sponsorship of Activities (September 1, 1968 - August 31, 1969)

<i>Sponsors</i>	<i>Number of Activities</i>	<i>Percent of Activities</i>	<i>Number of Hours</i>	<i>Percent of Hours</i>
Hospitals (32)*	89	14.4	943.0	12.2
Medical Schools (8)	315	50.8	3,756.5	48.7
Specialty Societies (55)	74	11.9	1,071.0	13.9
Voluntary Health Agencies (23)	30	4.8	266.0	3.5
Other† (21)	112	18.1	1,666.5	21.6
Totals	620	100.0	7,703.0	100.0

\*Number of sponsors reporting activities.

†Includes California Regional Medical Programs, California Medical Association, County Medical Societies and Research Foundations.

TABLE 4.—Continuing Medical Education Activities in Medical Schools in Comparison with Total Continuing Medical Education Activities (September 1, 1968 - August 31, 1969)

<i>Medical Schools</i>	<i>Number of Activities</i>	<i>Percent of Total</i>	<i>Number of Hours</i>	<i>Percent of Total</i>
Loma Linda University	2	.6	65.0	1.7
Stanford University	11	3.5	225.5	6.0
University of California, Davis	1	.3	56.0	1.5
University of California, Irvine	3	1.0	109.0	2.9
University of California, Los Angeles	103	32.7	812.5	21.6
University of California, San Diego	3	1.0	137.0	3.6
University of California, San Francisco	150	47.6	1,506.0	40.1
University of Southern California	42	13.3	845.5	22.5
Totals	315	100.0	3,756.5	100.0

TABLE 5.—Continuing Medical Education Activities by Specialties and Selected Categories Listed in Order by Number of Hours (September 1, 1968 - August 31, 1969)

<i>Specialties and Selected Categories</i>	<i>Number of Activities</i>	<i>Percent of Activities</i>	<i>Number of Hours</i>	<i>Percent of Hours</i>
Medicine	211	34.0	3,060.5	39.7
Surgery	106	17.1	1,272.5	16.5
Psychiatry	63	10.2	850.5	11.0
Pediatrics	54	8.7	785.5	10.2
General Practice	63	10.2	582.5	7.6
Mental Retardation	8	1.3	301.5	3.9
Obstetrics and Gynecology	19	3.1	218.0	2.8
Radiology	15	2.4	156.5	2.0
Cancer	33	5.3	118.5	1.5
Basic Sciences	9	1.4	114.0	1.5
Business Aspects of Medical Practice	9	1.4	62.5	.8
Adolescent Medicine	11	1.8	60.5	.8
Industrial, Occupational and Environmental Medicine	8	1.3	51.5	.7
Alcoholism and Drug Use	5	.8	26.0	.3
Aviation Medicine	2	.3	25.5	.3
Social and Community Medicine	4	.6	17.0	.2
Totals	620	100.0	7,703.0	100.0

lished summary, but not shown here] that only two continuing medical education activities on the subject of trauma were offered during the 1968-69 year. However, instruction in this subject was given in some of the General Surgery and General Practice courses. The CMA's Bureau of Research and Planning on behalf of the Committee on Continuing Medical Education is currently conducting a census of continuing medical education. The results, which should be published sometime next year, will give long awaited information as to how many and what specialties of physicians avail themselves of what types of educational opportunities afforded them.

It should be noted that the categorization of some courses into specialties and selected categories is difficult. Efforts continue, however, to

develop a method to better standardize the reporting of activity content and hours.

With the advent of the American Medical Association's accreditation of continuing medical education sponsors, and with similar accreditation by CMA on the horizon, plus the CMA's Certificate in Continuing Medical Education, it becomes increasingly important for prospective sponsors to be accurately informed on an activity's content and number of instructional hours. In addition to publishing the Annual Summary of Continuing Medical Education in California and listing the activities monthly in the "Continuing Medical Education Activities" section of CALIFORNIA MEDICINE and quarterly in the *Medical Dates Bulletin*, the CMA currently has an information office that

centralizes information on all activities statewide and provides a clearinghouse service for sponsors. This office has an electrofile which stores, and makes available for immediate retrieval, data projected ahead three to five years on all California and Hawaii educational activities and nationwide major medical meetings. This information is available to any program sponsor. Sponsors then can avoid duplication of programs, choose a more appropriate date, and perhaps even plan to utilize speakers coming from a distance at a time near that of their own program.

The Continuing Medical Education Office is eager to be of assistance in providing information in as great detail as is available to assist sponsors

in their planning. To make available a comprehensive clearinghouse to all program purveyors, the cooperation of each is essential. Thus, each sponsor is urged to make plans as far in advance as possible and to send his tentative and final information immediately and regularly to the Continuing Medical Education Office (address below).

The 1968-69 Annual Summary was funded through a grant from the California Regional Medical Programs. Copies of the summary as well as more detailed breakdowns by specific activities are available on request to the Committee on Continuing Medical Education, California Medical Association, 693 Sutter Street, San Francisco, Ca. 94102.

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# PUBLIC HEALTH REPORT

Louis F. Saylor, M.D., M.P.H., Director, State Department of Public Health

## Venereal Disease in California

CALIFORNIA HAS THE fourth highest venereal disease (VD) rate in all 50 states and San Francisco the second highest rate among cities in the nation. In 1969 reported VD cases topped the 100,000 mark for the first time in the state's history, with 11,000 cases of syphilis and 90,000 of gonorrhea. It was the eighth consecutive year that VD headed the list of notifiable communicable diseases.

Last year 241 cases of congenital syphilis were reported. More than 500 syphilitic insane persons are cared for in California's mental health hospitals at an annual cost of \$3 million. California taxpayers also spend over half a million dollars annually to aid the syphilitic blind.

It is estimated that this year the actual (as distinct from reported) number of VD cases will be 500,000. One in ten Californians under 25 will have VD this year and this age group will account for over half the state's cases. Many are repeaters. In some areas 20 percent of the high school students will have VD before graduation and in a few high-incidence areas more than 50 percent will become infected.

Using federal funds the State Department of Public Health conducts an effective statewide program primarily to prevent and control syphilis. A state core staff of 11 persons and 55 locally assigned workers provide case-finding services to 53 counties and medical and education services to all 58.

Venereal disease workers visit public and private laboratories to enlist their help in reporting all reactive tests for syphilis. They follow up test results to ensure that infected persons receive treatment and to locate the source and the spread contacts for new cases. They visit practicing physicians to acquaint them with the VD program, to offer available health department facilities, services and consultation and to encourage prompt reporting and interviewing of VD cases. Local health departments provide VD clinics and some work closely with "free clinics" which are springing up throughout the state.

The state VD workers direct an educational pro-

gram to teachers of junior and senior high school students. They carry on information and education activities through television, radio and the press and with public and voluntary agencies. Professional education activities are directed to physicians and hospitals, departments of health and schools of medicine, nursing and public health.

Since 1962, when President Kennedy's Task Force on Syphilis reported, federal funds and personnel have been available for syphilis control. The U.S. Public Health Service, in cooperation with state and local health departments, began a concentrated attack on this disease. The attack is reflected in a significant downward trend since 1963.

Neither federal funds nor personnel are assigned to the control of gonorrhea, the most common of the venereal diseases and the only one increasing in California. Over the past decade, the incidence of gonorrhea has increased three-fold. The complications of gonorrhea include arthritis, sterility, urethritis, prostatitis, gonorrheal conjunctivitis of the newborn and occasionally death. Thousands of women are admitted to hospital each year for pelvic inflammatory disease and many require hysterectomy because of chronic gonorrhea. Direct medical costs for treatment of gonorrhea in California, not including the late medical consequences of the disease, are conservatively estimated at \$6.5 million.

Many of the methods used to control syphilis can be applied to gonorrhea although the short incubation of the latter makes control of transmission more difficult. Recent laboratory research includes work on a new serologic screening test for gonorrhea which may soon be available to detect asymptomatic cases. Judging from frequent findings of unsuspected disease in pelvic examinations, asymptomatic gonorrhea is increasing. Surveys have shown that 3 to 11 percent of laboratory cultures are positive for gonorrhea in women who have pelvic examinations in general clinics, including planned parenthood and prenatal clinics.

A number of private physicians consider screening of women for gonorrhea important enough to study means of implementing the procedure in



private medical practice. Carbon dioxide incubators help make gonorrheal cultures less expensive and more practical for physicians. Small incubators for offices utilize candles to obtain low oxygen tension and are adaptable for culturing gonococci.

Last year the California Legislature amended Section 4322, Business and Professions Code, to permit physicians and public health officers to give prophylactic advice for prevention of VD. Venereal disease clinics now give such advice, including use of a condom during sexual relations, and the advisability of washing with soap and water immediately after, and douching before and after sexual relations.

The biggest obstacles to VD control are public apathy and misplaced morality. Many persons, including professionals, believe that VD is as in-

evitable as death and taxes. Many others look upon VD as a moral rather than a public health issue. Another barrier is reluctance on the part of physicians to provide "epidemiologic treatment" to persons known to have been exposed. Public health clinics treat such persons, and a few private physicians do so. Also, we desperately need vaccines against syphilis and gonorrhea. A vaccine against gonorrhea could bring a decided reduction in one or two years. Unfortunately, research into these vaccines has low priority.

As the campaign against syphilis demonstrates, VD can be reduced, but much greater public awareness and support are required. If the medical profession and public health authorities join with the people of the state in a strong effort, it will be possible to control these costly diseases as we have controlled other communicable conditions.

#### POLYMXIN B FOR PSEUDOMONAS EYE INFECTIONS

"I reported some years ago after a study in premature infants that the usual commercially prepared polymixin B eye drops are clinically less effective in treating pseudomonas eye infections than pure, freshly made up polymixin B which you get from taking the aerosporin powder and making it up 10,000 units per ml with saline and diluting it. I have had a number of discussions about this with the Burroughs-Wellcome people over the years. They could not understand why this would occur because almost all pseudomonas are so highly sensitive to polymixin B *in vitro* that 6.25 micrograms per ml of the drug will inhibit them and you get 100 times that much in the eye drops. However, they are beginning to admit that maybe some of the polymixin B is bound to the glass or the plastic in the container. . . . I believe that this concept will become accepted.

"In serious pseudomonas infections, we have had much better results with freshly made up polymixin B, at least in getting rid of the bacteria—maybe not in saving the eye, than with the commercial preparations. It doesn't make much difference to Burroughs-Wellcome because they make all forms of the polymixin B; they have no axes to grind in selling the drug. They are going to sell it one way or another as long as you use their product."

—ROBERT P. BURNS, M.D., Portland

Extracted from *Audio-Digest Ophthalmology*, Vol. 7, No. 3, in the Audio-Digest Foundation's subscription series of tape-recorded programs.

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# In Memoriam

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Persons wishing to do so may make contributions to the Physicians' Benevolence Fund to honor the memory of a member who has died. Members of the family will be notified that such a contribution has been made and the name of the donor will be supplied.

Checks should be addressed to Physicians' Benevolence Fund, Inc., California Medical Association, 693 Sutter Street, San Francisco, Ca. 94102.

BEECH, ROBERT DECKER, Fresno. Died January 4, 1970 in Fresno of carcinoma, aged 56. Graduate of Northwestern University Medical School, 1940. Licensed in California in 1955. Doctor Beech was a member of the Fresno County Medical Society.

BURKLAND, CARL E., Sacramento. Died March 18, 1970 in Sacramento of heart disease, aged 61. Graduate of Johns Hopkins University School of Medicine, Baltimore, 1935. Licensed in California in 1941. Doctor Burkland was a member of the Sacramento County Medical Society.

DOCKHAM, CHARLES WILLIAM, Los Angeles. Died March 1, 1970 in Alhambra, aged 60. Graduate of the College of Medical Evangelists, Loma Linda-Los Angeles, 1941. Licensed in California in 1941. Doctor Dockham was a member of the Los Angeles County Medical Association.

EVANS, PAUL HANNING, Los Angeles. Died March 24, 1970 in Mexico in an airplane crash, aged 48. Graduate of University of Tennessee College of Medicine, Memphis, 1946. Licensed in California in 1949. Doctor Evans was a member of the Los Angeles County Medical Association.

FAWCETT, JOHN HUBERT, Indio. Died February 22, 1970 in San Bernardino of injuries received in an automobile crash, aged 39. Graduate of McGill University Faculty of Medicine, Montreal, 1959. Licensed in California in 1960. Doctor Fawcett was a member of the Riverside County Medical Association.

GEARY, JOHN R., JR., Mill Valley. Died March 3, 1970 in Mill Valley, aged 50. Graduate of the University of Rochester School of Medicine and Dentistry, New York, 1943. Licensed in California in 1952. Doctor Geary was a member of the Marin Medical Society.

GLEW, EUGENE L., Los Angeles. Died March 10, 1970 in Glendale of cerebral vascular accident, aged 64. Graduate of the College of Osteopathic Physicians and Surgeons, Los Angeles, 1937. Licensed in California in 1937. M.D. degree from California College of Medicine, 1962. Doctor Glew was a member of the Los Angeles County Medical Association.

IGRA, LUDWIG, Oakland. Died March 7, 1970 in Oakland of acute myocardial infarction, aged 55. Graduate of the University of Illinois College of Medicine, Chicago, 1945. Licensed in California in 1948. Doctor Igra was a member of the Alameda-Contra Costa Medical Association.

JOHNSON, CLARENCE E., Long Beach. Died February 23, 1970 in Long Beach, aged 72. Graduate of Rush Medical College, Chicago, 1923. Licensed in California in 1928. Doctor Johnson was a member of the Los Angeles County Medical Association.

LEE, FRANK WARNE, Sacramento. Died March 13, 1970 in Sacramento, aged 71. Graduate of University of California Medical School, Berkeley-San Francisco, 1923. Licensed in California in 1923. Doctor Lee was a member of the Sacramento County Medical Society.

NORTH, ELMER F., JR., Sunnyvale. Died March 12, 1970 in Mountain View, aged 40. Graduate of George Washington University School of Medicine, Washington, D.C., 1956. Licensed in California in 1957. Doctor North was a member of the Santa Clara County Medical Society.

PATTERSON, EDNA F., St. Helena. Died November 6, 1969 in St. Helena of carcinoma of the breast, aged 79. Graduate of the College of Medical Evangelists, Loma Linda-Los Angeles, 1917. Licensed in California in 1917. Doctor Patterson was a retired member of the Yolo County Medical Society and the California Medical Association, and an associate member of the American Medical Association.

QUIMBY, SMITH A., Madera. Died November 30, 1969 in Madera of cerebral thrombosis, aged 81. Graduate of the University of Vermont College of Medicine, Burlington, 1915. Licensed in California in 1921. Doctor Quimby was a member of the Fresno County Medical Society.

RIGHETTI, ETHEL LUCIA, Castro Valley. Died February 28, 1970 in Castro Valley, aged 77. Graduate of the University of California Medical School, Berkeley-San Francisco, 1918. Licensed in California in 1918. Doctor Righetti was a retired member of the San Francisco Medical Society and the California Medical Association, and an associate member of the American Medical Association.

SAVIONI, AMERICO JOSEPH, Sacramento. Died March 22, 1970 in Sacramento of heart disease, aged 46. Graduate of College of Osteopathic Physicians and Surgeons, Los Angeles, 1955. Licensed in California in 1955. M.D. degree from California College of Medicine, 1962. Doctor Savioni was a member of the Sacramento County Medical Society.



# CONTINUING MEDICAL EDUCATION ACTIVITIES IN CALIFORNIA AND HAWAII (FORMERLY WHAT GOES ON)

## COMMITTEE ON CONTINUING MEDICAL EDUCATION

THIS BULLETIN of information regarding continuing education programs and meetings of various medical organizations in California and Hawaii is supplied by the Committee on Continuing Medical Education of the California Medical Association. In order that they may be listed here, please send communications relating to your future meetings or postgraduate courses to Committee on Continuing Medical Education, California Medical Association, 693 Sutter Street, San Francisco 94102; or phone: (415) 776-9400, extension 241.

## ALCOHOLISM AND DRUG USE

May 16 & 23—**The Drug Scene.** University of California Extension, Riverside, at 1500 Life Sciences Building, UC Riverside. Two Saturdays. Primarily for physicians. 14 hrs. Contact: Ray Olitt, Health Services Program Coordinator, UC Extension, Riverside 92502. (714) 787-4329.

## CANCER

May 15-16 — **Hormones and Neoplasms—Cancer Conference.** USC at Century Plaza Hotel, Los Angeles. Friday-Saturday. Relationships between hormones and neoplasms, emphasis on hormone producing tumors, exclusive of those of ovarian or testicular origin. Current methodology in diagnosis of such tumors, therapeutic principles. \$40. 12 hrs.

## MEDICINE

May 15—**California Heart Association—Annual Meeting Scientific Sessions.** Hotel del Coronado, Coronado. Friday. Coronary thrombosis and myocardial infarction, problems in ECG diagnosis of myocardial infarction, premature coronary disease, coronary arteriography. \$10. 7 hrs. Contact: Rodman D. Starke, M.D., 1370 Mission St., San Francisco 94103. (415) 626-0123.

May 15 — **Physical Signs in Cardiovascular Disease (Clinical Problems in Valvular Heart Disease).** STAN, Santa Clara and San Mateo Heart Associations, and CRMP Area III at Palo Alto Veterans Administration Hospital, Palo Alto. Friday. Review of important physical signs of cardiovascular disease. A.M., examination of cardiac patients; P.M., systematic review of physiological basis and implications of salient physical signs. \$5. 8 hrs. Contact: Herbert Hultgren, M.D., Medical Service (III), Palo Alto V.A. Hospital, 3801 Miranda Ave., Palo Alto 94306. (415) 326-5600.

May 15-17—**Basic Principles of Cardiac Therapy.** PMC and the American College of Cardiology at Jack

Tar Hotel, San Francisco. Friday-Sunday. Clarification of pathophysiological basis of various disease states, rational approach to drug usage. \$80 members, \$120 non-members. 24 hrs. Contact: PMC.

May 16—**Progress and Problems in Neurology for the '70s.** Palo Alto Medical Clinic and Research Foundation, Palo Alto. Saturday. Treatable Forms of Dementia; Mechanisms of Developmental Defects of the Nervous System; New Concepts of "Degenerative" Neurological Diseases—The Role of Slow Viruses; The Medical and Neurological Implications of Space Travel; Recent Advances in Adult Neurology—Parkinsonism and DOPA; "Pot" and "Acid" — The Medical and Neurological Implications of the Drug Problem; The Current Status of Strokes and Anticoagulation; Senile Neuronal Drop-Out — The Problems of Growing Old Gracefully. \$15. 5½ hrs. Contact: Bernard I. Lewis, M.D., Palo Alto Medical Clinic and Research Foundation, 300 Homer Ave., Palo Alto 94301. (415) 321-4121.

## KEY TO ABBREVIATIONS AND SYMBOLS

Medical Centers and CMA Contacts  
for Information

- CMA:** California Medical Association  
Contact: Continuing Medical Education, California Medical Association, 693 Sutter Street, San Francisco 94102. (415) 776-9400, ext. 241.
- LLU:** Loma Linda University  
Contact: John E. Peterson, M.D., Associate Dean for Research Affairs, Loma Linda University School of Medicine, Loma Linda 92354. (714) 796-7311.
- PMC:** Pacific Medical Center  
Contact: Arthur Selzer, M.D., Chairman, Education Committee, Pacific Medical Center, Clay and Webster Streets, San Francisco 94115. (415) 931-8000.
- STAN:** Stanford University  
Contact: John L. Wilson, M.D., Chairman on Postgraduate Education, Stanford University School of Medicine, 300 Pasteur Drive, Stanford 94305. (415) 321-1200, ext. 5594.
- UCD:** University of California, Davis  
Contact: George H. Lowrey, M.D., Professor and Chairman, Department of Postgraduate Medicine, University of California, Davis, School of Medicine, Davis 95616. (916) 752-0331.
- UCI:** University of California — California College of Medicine, Irvine  
Contact: Robert Combs, M.D., Associate Dean, University of California, Irvine—California College of Medicine, Irvine 92664. (714) 833-5991.
- UCLA:** University of California, Los Angeles  
Contact: Donald Brayton, M.D., Associate Dean and Head, Continuing Education in Medicine and the Health Sciences, 15-39 Rehabilitation Center, UCLA Center for the Health Sciences, Los Angeles 90024. (213) 825-6514.
- UCSD:** University of California, San Diego  
Contact: Michael Shimkin, M.D., Associate Dean for Health Manpower, 1309 Basic Sciences Building, University of California, San Diego, School of Medicine, La Jolla 92038. (714) 463-2000, ext. 2704.
- UCSF:** University of California, San Francisco  
Contact: Seymour M. Farber, M.D., Dean, Educational Services and Director, Continuing Education, Health Sciences, University of California Medical Center, San Francisco 94122. (415) 666-1692.
- USC:** University of Southern California  
Contact: Phil R. Manning, M.D., Associate Dean, Postgraduate Division, University of Southern California School of Medicine, 2025 Zonal Avenue, Los Angeles 90033. (213) 225-1511, ext. 203.



May 16-17—**Current Concepts on the Management of the Stroke Patient.** Granada Hills Community Hospital and San Fernando Valley State College Health Sciences Department at Main Auditorium, Speech Building, San Fernando Valley State College, Los Angeles. Saturday-Sunday. Management and Rehabilitation; Role of Anticoagulants; Psychological and Psychiatric Problems; Cerebral-Vascular Accidents in the Young; Headache; Subclavian Steel Syndrome; Extra- and Intra-Cranial Hemodynamic Flow Studies; Echo-Encephalography; Electro-Encephalography; Brain Scanning; Role of Extra-Cranial Vascular Surgery; Angiography. \$10. 16 hrs. Contact: Arno A. Roscher, M.D., Program Chairman, Granada Hills Community Hospital, 10445 Balboa Blvd., Granada Hills 91344. (213) 360-1021.

May 22-23—**Instrumental Acquisition of Cardiological Data with Clinical Correlation.** American College of Cardiology, Memorial Hospital of Long Beach, and Long Beach Heart Association at Memorial Hospital of Long Beach. Friday-Saturday. Precordial scintillation scanning; special catheters for ventricular function studies; thermodilution flowmeters; external measurements for ventricular function; new methods of cardiac pacing; use of vectorcardiography for infarct sizing. \$55. 14 hrs. Contact: William D. Nelligan, Exec. Dir., ACC, 9650 Rockville Pike, Bethesda, Md. 20014. (301) 530-1600.

May 23—**Infectious Problems in Renal Disease.** USC. Saturday. \$25. 6 hrs.

May 25-28—**International Conference on Vascular Diseases of the Brain and Spinal Cord.** American Academy of Neurology, USC and Rancho Los Amigos Hospital at Anaheim Convention Center, Anaheim. Monday-Thursday. U.S. and international papers, rehabilitation team personnel invited. Limited traineeships available. \$125. 18 hrs. Contact: Richard P. Boggs, M.D., Chief, Division of Neurological Sciences, Rancho Los Amigos Hospital, 7601 E. Imperial Highway, Downey 90242. (213) 869-0921.

June 1-12—**Coronary Care Unit Program for Physicians.** CRMP Area V at Los Angeles County-USC Medical Center. Two week course repeated monthly through June, 1970. Arrhythmia detection, diagnosis and therapy, defibrillation and cardioversion, central venous pressure monitors, placement of pacing catheters, new aspects in diagnosis and treatment of congestive heart failure, shock and associated respiratory problems, and CCU management in community hospitals. Contact: Gladys Ancrum, Dr. P. H., Administrative Associate, CRMP Area V, 1 West Bay State St., Alhambra 91801. (213) 576-1626.

June 5—**Newer Clinical Applications of Electrocardiography.** UCSF at Mt. Zion Hospital and Medical Center. Friday-Saturday. Monitoring the Ambulance, the Hospitalized Patient, the Surgical Patient, the Exercising Patient, and the Ambulatory Patient; Correlation of ECG to Clinical Medicine; The ECG in Metabolic Diseases, in Pulse Recording, in Pacemaker Evaluation, in Computers; Practical Aspects of Hospital Electrocardiography. 5½ hrs.

June 15-July 3—**Coronary Care for Physicians Training Program.** CRMP Area IV and Cedars-Sinai Medical Center at Cedars of Lebanon Hospital, Los Angeles. Three week course repeated six times through Novem-

ber, designed for practicing internists or cardiologists who will subsequently be working in or directing CCU in community hospitals. Electrocardiography, physical diagnosis, CCU planning and administration, electrolytes and acid-base metabolism, emphasis on practical techniques. Contact: Herbert Stein, M.D., Coronary Care for Physicians Training Programs, Dept. of Cardiology, Cedars of Lebanon Hospital, Box 54265, Los Angeles 90029. (213) 662-9111, ext. 306.

June 17-18—**Exercise in Coronary Disease.** USC at Rancho Los Amigos Hospital, Downey. Wednesday-Thursday. 12 hrs.

June 22-23—**American Diabetes Association—Annual Meeting Scientific Session.** Sheraton-Palace Hotel, San Francisco. Monday-Tuesday. Contact: J. Richard Connelly, Exec. Dir., 18 E. 48th Street, New York 10017. (212) 752-8550.

August 16-19—**The Thirteenth Annual Advanced Seminar on Internal Medicine.** UCLA at UCLA Residential Conference Center, Lake Arrowhead. Sunday-Wednesday.

Continuously—**Basic Home Course in Electrocardiography.** One year postgraduate series, ECG interpretation by mail. Physicians may register at any time. \$100 (52 issues). Contact: USC.

Continuously—**Training in the Procedure of Tonometry.** Northern California Society for the Prevention of Blindness at the Glaucoma Screening Clinic, San Francisco. Weekly Saturday morning program in tonometry for internists and general practitioners. Advance appointment required, no charge. 3 hrs. Contact: Frederic S. Weisenheimer, Ed.D., Exec. Dir., NCSBP, 4200 California Street, San Francisco 94118. (415) 387-0934.

Continuously — **Medico-Surgical Cardiovascular Seminar.** Palo Alto Veterans Administration Hospital, Palo Alto. First Thursday of each month, lectures, demonstrations, seminar discussions, and rounds. Designed specifically for a selected group of physicians from the Fresno area. Other physicians invited to participate. Contact: William Angell, M.D., Division of Cardiovascular Surgery, Dept. of Surgery, Palo Alto V.A. Hospital, 3801 Miranda Avenue, Palo Alto 94306. (415) 326-5600.

Continuously—**Coronary Care Unit Training for Physicians.** CRMP Area VI and San Bernardino County General Hospital at San Bernardino County General Hospital. Four week courses at monthly intervals, scheduled by arrangement. For practicing physicians working in and directing CCU's. Bedside care, electrocardiography, physical diagnosis, clinical history, therapy, insertion of pacemakers, cardioversion. 160 hrs. Contact: Carl L. Cook, Jr., M.D., San Bernardino County General Hospital, 780 E. Gilbert St., San Bernardino 92404. (714) 885-3411.

Continuously—**Training for Physicians in Nephrology.** CRMP Area VI and LLU at LLU. Courses of four weeks or more available, to be scheduled by arrangement. Bedside conferences, clinical care and management. Hemodialysis, peritoneal dialysis, renal biopsy and kidney transplantation. 160 hrs. Contact: Stewart W. Shankel, M.D., LLU.

Continuously—**Training for Physicians in General Internal Medicine.** CRMP Area VI and LLU at LLU.

Four weeks or more, scheduled by arrangement. Bed-side and classroom training, practical aspects of clinical care and management. 160 hrs. Contact: LLU.

**Continuously—Training of Physicians in Modern Concepts of Pulmonary Care.** CRMP Area VI, LLU and Riverside General Hospital. Four weeks or more, scheduled by arrangement. Diagnostic and therapeutic methods in medical chest disease, physiological methodology of modern pulmonary care programs, use of new instrumentation in the field. 160 hrs. Contact: George G. Burton, M.D., LLU.

#### **Grand Rounds—Medicine**

##### **Tuesdays**

8:30-10:00 a.m., Assembly Hall, Harbor General Hospital, Torrance. UCLA.

##### **Wednesdays**

10:30-12:00 noon. Auditorium, Medical Sciences Building. UCSF.

11:00 a.m., Room 1645, Los Angeles County-USC Medical Center. USC.

12:30 p.m., Auditorium, School of Nursing, Orange County Medical Center. UCI.

12:30-1:30 p.m., University Hospital, UCSD.

##### **Thursdays**

10:30-12:00 noon, Room 33-105, UCLA Medical Center. UCLA.

##### **Fridays**

8:00 a.m., Courtroom, Third Floor, Kern County General Hospital, Bakersfield. CRMP Area IV.

8:30 a.m., Auditorium, Lebanon Hall, Cedars of Lebanon Hospital, Los Angeles. CRMP Area IV.

Neurology. 10:15 a.m., held alternately at Stanford University Hospital and Neurology Conference Building 7, V.A. Hospital, Palo Alto. STAN.

1st and 3rd Fridays, 11:00 a.m., Auditorium, Brown Building, Mount Sinai Hospital, Los Angeles. CRMP Area IV.

1:15 p.m., Lieb Amphitheater, Timken-Sturgis Research Bldg., La Jolla. Scripps Clinic and Research Foundation.

Rheumatology Grand Rounds. 11:45 a.m., Room 6441, Los Angeles County-USC Medical Center, Los Angeles. USC.

#### **MENTAL RETARDATION**

**June 8-19—Mental Retardation Workshop.** UCLA and Pacific State Hospital, Pomona, at UCLA Neuropsychiatric Institute. Two weeks. For physicians and allied professionals. Causation, symptomatology, care, treatment and management, diagnostic techniques suitable for office practice, parental reactions and intra-family psychopathology, recent research findings. 80 hrs. Contact: UCLA.

#### **OBSTETRICS AND GYNECOLOGY**

**May 15-16—Obstetrics and Gynecology Symposium.** Southern California Permanente Medical Group and Kaiser Foundation Hospitals at Beverly Hilton Hotel, Beverly Hills. Friday-Saturday. Contact: Shirley Gach, Rm. 6014, So. Calif. Permanente Med. Group, 4900 Sunset Blvd., Los Angeles 90027. (213) 663-8411.

**August 9-12—The Third Annual UCLA Seminar on Obstetrics and Gynecology.** UCLA at UCLA Residential Conference Center, Lake Arrowhead. Sunday-Wednesday.

#### **Grand Rounds—Obstetrics and Gynecology**

##### **Mondays**

10-11:30 a.m., Assembly Room, First Floor, Harbor General Hospital, Torrance. UCLA.

##### **Fridays**

8 a.m., Auditorium, Orange County Medical Center. UCI.

#### **PEDIATRICS**

**May 16-17—American Academy of Pediatrics—Northern California Chapter.** Four Seasons, Tahoe City. Saturday-Sunday. Light Therapy for Hyperbilirubinemia and Intensive Care in the Nursery; Serious Infections in the Newborn; Genetic Disorders of Metabolism; Cardiac Transplantation; Environmental and Population Problems. \$20. 8 hrs. Contact: Birt Harvey, M.D., 1101 Welch Road, Palo Alto 94304. (415) 325-4482.

**May 18-19—Hearing Problems in Children—Recent Advances.** UCLA. Monday-Tuesday. Recent advances in basic auditory psychophysics, seminars on auditory measurements in the infant and young child, special pediatric diagnostic techniques, genetic aspects of pediatric deafness, rubella deafness. Rh deafness in children, pediatric dysacusis, rehabilitation and education of the hard of hearing and of the deaf child. \$75. 12 hrs.

**May 20-21—Otitis-Mastoiditis in Children.** UCLA. Wednesday-Thursday. Problem of serous otomastoiditis and the "glue ear." Pediatric, allergic, immunopathologic and oto-surgical points of view. Complications of non-responsive mastoiditis—local, constitutional, and intracranial; tympanoplasty; specific problems of otitis perforata, traumatic and infectious; noncholesteatomatous mastoiditis; cholesteatoma. \$75. 12 hrs.

**June 5—Annual Premature Day.** STAN. Friday. \$15. 5½ hrs.

**June 19-21—Southern California Postgraduate Meeting.** Childrens Hospital of Orange County. Friday-Sunday. Neonatology; Genetics and Inborn Errors of Metabolism; Growth and Endocrinology; Gastroenterology and Shock. \$35. 17 hrs. Contact: Merl J. Carson, M.D., Childrens Hospital of Orange County, 1109 W. La Veta, Orange 92668. (714) 538-8831.

**June 24-26—Annual Pediatric Seminar—The First Ten Months of Life.** Childrens Health Center, San Diego. Wednesday-Friday. \$25. 15 hrs. Contact: David L. Chadwick, M.D., Medical Director, 8001 Frost Street, San Diego 92123. (201) 277-5808.

#### **Grand Rounds—Pediatrics**

##### **Tuesdays**

8:00 a.m., Childrens Hospital Medical Center, Oakland.

8:30 a.m., Auditorium, Childrens Division Building, Los Angeles County-USC Medical Center, Los Angeles. USC.



8:30 a.m., Room 4-A, Kern County General Hospital, Bakersfield. CRMP Area IV.

8:30 a.m., Pathology Auditorium, San Francisco General Hospital.

#### Wednesdays

8-9:00 a.m., held alternately at Auditorium, Orange County Medical Center and Auditorium, Childrens Hospital of Orange County. UCI.

8:30 a.m., Bothin Auditorium, Childrens Hospital, San Francisco.

#### Thursdays

8:30-10:00 a.m., Room 664, Science Building, UCSF.

8:30-9:30 a.m., Lebanon Hall, Cedars of Lebanon Hospital, Los Angeles.

8:30 a.m., First Floor Auditorium, Harbor General Hospital, Torrance.

#### Fridays

8:00 a.m., Lecture Room, A Floor, Health Sciences Center, UCLA. CRMP Area IV.

8:30 a.m., Room M104, Stanford University Medical Center, Stanford.

8-9:00 a.m., Lecture Hall, Childrens Hospital of Los Angeles.

Infectious Disease Grand Rounds. 10:00 a.m., Auditorium, Childrens Division Building, Los Angeles County-USC Medical Center, Los Angeles. USC.

### PSYCHIATRY

May 16-17—**The Archipelago of Psychotherapy.** UCSF at Napa State Hospital, Imola. Saturday-Sunday. Auspicious Healing; Psychoanalysis of Schizophrenic Psychoses and Certain Characterological Disorders; Psychodrama; Family Therapy; Behavior Therapy; Transactional Analysis; Encounter Groups; Gestalt Therapy; Hypnosis and Operational Psychotherapy. \$15. 11½ hrs.

May 23-24—**Anxiety and Depression.** UCSF at DeWitt State Hospital, Auburn. Saturday-Sunday.

June 26-28—**Comparative Psychotherapies.** USC Division of Postgraduate Psychiatry at Sahara Tahoe Hotel, Lake Tahoe. Friday-Sunday. \$35. Contact: Donald F. Naftulin, M.D., Director, Division of Postgraduate Psychiatry, USC. (213) 225-1511, ext. 336.

### RADIOLOGY—PATHOLOGY

May 16—**Radiology Society of Southern California.** Hotel del Coronado, Coronado. Saturday. Contact: Gladden V. Elliott, M. D., 5565 Grossmont Center Drive, Suite 1, La Mesa 92041.

Continuously—**Principles and Clinical Uses of Radioisotopes.** UCSF. Fundamentals for the proper understanding and use of radioactivity in clinical medicine. Training in diagnostic and therapeutic uses of radioisotopes. Normal period of training: 3 months. Two part course: Part A, Basic Fundamentals; Part B, Clinical Applications.

Continuously — **Mammography.** UCSF Mammography Section, Department of Radiology. Three days weekly, beginning with Tuesday. Call several days in advance.

Contact: Richard H. Gold, M.D., Mammography Section, Department of Radiology, UCSF. (415) 666-1918.

### Grand Rounds—Radiology

#### Fridays

Neuroradiology Grand Rounds. 9:30 a.m., held alternately at Stanford University Hospital and Neurology Conference Building 7, V.A. Hospital, Palo Alto, STAN.

### SURGERY—ANESTHESIOLOGY

May 18-19—**Hearing Problems in Children — Recent Advances.** See Pediatrics, May 18-19.

May 20-21—**Otitis-Mastoiditis in Children.** See Pediatrics, May 20-21.

June 4-6—**Highlights of Ophthalmology.** PMC Department of Ophthalmology at PMC. Thursday-Saturday. Cryosurgery, Fluorescein angiography, glaucoma, cataract surgery, diabetic retinopathy, retinal detachment, adhesives in surgery, contact lenses and ultrasonography. \$125. Contact: Wayne L. Erdbrink, M.D., Director of Residency Training, Dept. of Ophthalmology, PMC.

June 4-6—**Rheumatoid Arthritic Surgery.** UCSF and American Academy of Orthopaedic Surgeons at UCSF. Thursday-Saturday. \$150. 17½ hrs. Contact: UCSF.

June 12-13—**Le Roy C. Abbott Orthopedic Society—Annual Meeting.** University of California Hospital, San Francisco. Friday-Saturday. 8 hrs. Contact: William S. Cappeller, M.D., Sec.-Treas., LCAOS, 450 Sutter Street, San Francisco 94108. (415) 397-4455.

June 12-14—**California Society of Anesthesiologists—4th Biennial Scientific Meeting.** Sahara-Tahoe Hotel, South Shore, Lake Tahoe. Friday-Sunday. The Anesthesiologist and Emergency Care; Preoperative Evaluation of the Surgical Patient. 8 hrs. \$30 members, \$40 non-members. Contact: Norman R. Catron, Exec. Sec., CSA, 100 So. Ellsworth Ave., Suite 401, San Mateo 94401. (415) 343-4644.

June 25-27—**1970 Stanford Ophthalmology Conference.** STAN. Thursday-Saturday. Diseases of conjunctiva and cornea, retina and choroid, practical aspects of ocular physiology and bacteriology. \$100. 17 hrs. Contact: Jerome Bettman, M.D., Division of Ophthalmology, A227, Dept. of Surgery, STAN.

July 1-August 29—**Stanford Basic Course in Ophthalmology.** STAN. Two months. Sections in Biochemistry, Physiology, Embryology and Genetics, Microbiology and Immunology, Neuro-ophthalmology and Neuroanatomy, Optics and Theory of Refraction, Motility, Pharmacology and Toxicology. \$550. 227½ hrs. Contact: Jerome Bettman, M.D., Division of Ophthalmology, A227, Dept. of Surgery, STAN.

July 5-17—**Temporal Bone Dissection Course.** Los Angeles Foundation of Otolaryngology, Los Angeles. Two week course demonstrating multiple approaches to structures of the temporal bone. Televised surgery correlated with dissections, lectures and motion picture demonstrations. Dissection in temporal bone laboratory over closed circuit television, student supervision. \$1,000 Otolaryngologists, \$500 Residents. 106 hrs. Course repeated in October, 1970. Contact: Jack L. Pulec, M.D., Los Angeles Found-



dition of Otology, 2130 W. Third St., Los Angeles 90057. (213) 483-4431.

**July 18—Clinical Electronystagmography Course.** Los Angeles Foundation of Otology, Los Angeles. Saturday. Physicians urged to bring ENG Technician for special instruction. Anatomy and Physiology of Vestibular System, Demonstration of Technique of Vestibular Stimulation and ENG Recording and Calculation, Significance of and Interpretation of Electronystagmogram, Discussion of Cases, Vistas in Vestibular Investigation. \$60. 6½ hrs. Contact: Jack L. Pulec, M.D., Los Angeles Foundation of Otology, 2130 W. Third St., Los Angeles 90057. (213) 483-4431.

**July 30-August 1—Strabismus Conference.** PMC Department of Ophthalmology at PMC. Thursday-Saturday. Surgical Diagnosis and Treatment, Follow-up. Emphasis of surgical technique through motion picture. \$125. Contact: Wayne L. Erdbrink, M.D., Director of Residency Training, Dept. of Ophthalmology, PMC.

**August 3-5—The Knee in Sports.** American Academy of Orthopaedic Surgeons at Hilton Hotel, San Francisco. Monday-Wednesday. \$150. 20 hrs. Contact: Fred H. Behling, M.D., 300 Homer Avenue, Palo Alto 94301. (415) 321-4121.

**August 19-23—Advanced Seminar in Urology.** UCLA at UCLA Residential Conference Center, Lake Arrowhead. Wednesday-Sunday.

**August 26-28—Keratoplasty Conference.** PMC Department of Ophthalmology at PMC. Wednesday-Friday. Planned for practicing ophthalmologists, improvement of surgical technique in corneal transplants and other aspects of keratoplasty. \$125. Contact: Wayne L. Erdbrink, M.D., Director of Residency Training, Dept. of Ophthalmology, PMC.

### **Grand Rounds—Surgery**

#### **Wednesdays**

7:15 a.m., Auditorium, Kern County General Hospital, Bakersfield. CRMP Area IV.

1st and 3rd Wednesdays. 11:00 a.m., Auditorium, Brown Building, Mount Sinai Hospital, Los Angeles. CRMP Area IV.

#### **Thursdays**

Neurology and Neurosurgery Grand Rounds. 11:00-12:15. Room 663, Science Building, UCSF.

#### **Fridays**

1-2:00 p.m., Auditorium, Orange County Medical Center, Orange. UCI.

Neurosurgery. 11:15 a.m., held alternately at Stanford University Hospital and Neurology Conference Building 7, V.A. Hospital, Palo Alto, STAN.

#### **Saturdays**

8:00 a.m., Auditorium, 1st floor, University Hospital of San Diego County, San Diego. UCSD.

9:00 a.m., Room 73-105, Health Sciences Center, UCLA. CRMP Area IV.

8:30 a.m., Assembly Room, Harbor General Hospital, Torrance. CRMP Area IV.

### **OF INTEREST TO ALL PHYSICIANS**

**May 16-17—Economic Organization of the Physician.** UCSF at Hilton Hotel, San Francisco. Saturday-Sunday. The Need for Protection and Development of the Physician's Capital, Investments of the Physician, Operational Problems of the Medical Practice, The Professional Corporation. \$75. 12½ hrs.

**May 20—Medical Practices in Central America and Mexico.** Agnews State Hospital, San Jose. Wednesday. 1½ hrs. Contact: J. Elizabeth Jeffress, M.D., Agnews State Hospital, San Jose 95114. (408) 262-2100.

**May 22-23—Teenage Pregnancies.** USC at International Hotel, Los Angeles. Friday-Saturday. Medicine, Education, Law, Social Services. \$20. 12 hrs.

**May 22-23—Frontiers in Medicine: Redwood Tour.** Humboldt-Del Norte County Medical Society at Eureka Inn, Eureka. Friday-Saturday. Friday: Redwood Tour. Saturday: Symposium. Use of New Auxiliary Pump in Cardiogenic Shock, Use of Saphenous Bypass Procedure to Augment Coronary Flow, Post-infarctional Rehabilitation, Environment and Pollution. 3 hrs. Contact: Henry R. Frank, M.D., 615 11th St., Arcata 95521. (707) 822-2185.

**May 22-24—California Medical Assistants Association—Annual Convention.** International and Hilton Hotels, Los Angeles. Friday-Sunday. Contact: Kay Marsh, 7271 Katella Avenue #19, Stanton 90680. (714) 828-3525.

**May 29-July 1—Medical Centers of Europe.** USC. Five weeks. Visiting medical centers in Dublin, London, Amsterdam, Moscow, Vienna, Rome, Venice-Lido, Paris. \$275.

**June 17—Income Maintenance Predicated on Reproductive Responsibility: A New Approach To The Prevention of Mental Illness Due to Ignorance, Poverty, and Overcrowding.** Agnews State Hospital, San Jose. Wednesday. 1½ hrs. Contact: J. Elizabeth Jeffress, M.D., Agnews State Hospital, San Jose 95114. (408) 262-2100.

**June 18-July 9—Medical Centers of Africa 1970.** USC in Africa. Three weeks. Visiting Senegal, Ivory Coast, Ghana, Uganda, Kenya, Tanzania. \$1699.

June 21-25 — **American Medical Association.** Palmer House, Chicago. Sunday-Thursday. Contact: Ernest B. Howard, M.D., Exec. Vice-Pres., AMA, 535 N. Dearborn St., Chicago 60610. (312) 527-1500.

**July 15—The Tenth Annual UCLA Seminar for General Practitioners.** UCLA at UCLA Residential Conference Center, Lake Arrowhead. Wednesday-Sunday.

**July 5-6—Postgraduate Course on Liquid Scintillation.** UCSF. Sunday-Monday.

**July 7-10—International Conference on Liquid Scintillation.** UCSF. Tuesday-Friday.

**July 19—Medical Management and Rehabilitation of the Handicapped: A Symposium for Medical Assistants.** UCSF. Sunday. \$12.50.

July 20-24 — **Hospital Information Systems: Techniques and Applications.** University of Southern California at Olin Hall of Engineering, University of Southern California. Monday-Friday. Emphasis on use of computer techniques in intensive care units, diagnostic aids, clinical laboratories, patient care, medical research, multiphasic screening. \$275. 40 hrs. Contact: William D. Campbell, Noncredit Programs, Administration Building, Room 355, University of Southern California, University Park, Los Angeles 90007. (213) 746-2418.

August 15-26 — **Thirteenth Annual Postgraduate Refresher Course in Honolulu and Kauai.** USC and the University of Hawaii School of Medicine at Royal Hawaiian Hotel, Tripler General Hospital, Kauai Surf Hotel, Surf Rider Hotel, and Princess Kaiulani Hotel. One and a half weeks. Shock, Adolescence, Spatial ECG, Pharmacology, Psychiatry, Orthopedics, Endocrinology, Surgery, Cardiology, Arrhythmias, Obstetrics and Gynecology, Obesity, Neurology, Emergency Care, Diabetes, Medicine, Pediatrics. 26 hrs. Contact: USC.

August 23-27 — **American Society for Pharmacology and Experimental Therapeutics.** Stanford University, Stanford. Sunday-Thursday. Contact: Ellsworth B. Cook, Ph.D., 9650 Rockville Pike, Bethesda, Md. 20014. (301) 530-3200.

Continuously—**Audio-Digest Foundation.** A non-profit subsidiary of CMA. Twice-a-month tape recorded summaries of leading national meetings and surveys of current literature. Services by subscription in: General Practice, Surgery, Internal Medicine, Ob/Gyn, Pediatrics, Anesthesiology, Ophthalmology. Catalog of lectures and panel discussions in all areas of medical practice also available. Contact: Mr. Claron L. Oakley, Editor, 619 S. Westlake Ave., Los Angeles 90057.

## TELEVISION

**Southern California's Medical Television Network.** UCLA. Weekly broadcasts, Tuesdays 8:30 a.m. Contact: UCLA Medical Television. (213) 825-2071.

May 19—**Psoriasis.** British Broadcasting Corporation.

May 26—**Breakthroughs in Malignant Diseases.** Medical Television Network.

**Santa Clara County Medical Society's MD-TV.** Weekly broadcasts. Thursdays 8:30 p.m. Channel 54, Greater San Jose Area. Of educational value to both physicians and nurses. Contact: Roger Brown, Santa Clara County Medical Society, 700 Empey Way, San Jose 95128 (408) 286-5050.

## CMA Postgraduate Institutes and Circuit Courses

May 15-16 — **Redwood Regional Conference.** CMA, UCSF at Konocti Harbor Inn, Clear Lake. Friday-Saturday. The Anemic Patient and Musculoskeletal Disorders. \$20. 14½ hrs. Contact: CMA.

June 18-20—**Sacramento Valley Counties Regional Postgraduate Institute.** CMA, UCLA and Sacramento County Medical Society at Cal Neva Lodge, North Lake Tahoe. Thursday-Saturday. Cerebral Vascular Disease including Rehabilitation and the Surgical and Medical Management of Cardiac Disease, Delivery of Health Care in the '70s. \$20. 12 hrs. Contact: CMA.

## STERIODS FOR PSEUDOMONAS INFECTION IN THE EYE

"I think that steroids are certainly inadvisable at any time in pseudomonas eye infection, even if you do wish to try to prevent corneal scarring. There may be enough of the bacteria hanging around so that steroids should just be out. Rather than take a chance on a flare-up of a few persistent organisms because of steroids, you should just let the corneal scarring run its own course."

—ROBERT P. BURNS, M.D., Portland

Extracted from *Audio-Digest Ophthalmology*, Vol. 7, No. 3, in the Audio-Digest Foundation's subscription series of tape-recorded programs.



# The Crisis Treatment of Suicide

NORMAN TABACHNICK, M.D., *Los Angeles*

■ *Almost all suicidal persons who consult physicians wish to live. Generally they fall into one of two groups. Interpersonal suiciders manifest frequent threats and attempts, are emotionally labile, have ill-defined suicide plans, and clear ideas as to how their crises might be resolved. Intrapersonal suiciders are less open in manifestations of suicidal drive, withdrawn rather than emotional, often have clearly-formulated suicide plans and do not have ideas (other than suicide) as to how their crises might end. The suicidal situation results from two factors: (1) the loss of some valuable person or commodity, and (2) the loss of self-esteem. What ensues is temporary character disorganization—crisis. Treatment is based on restoration or replacement of lost objects and building up of self-esteem.*

SUICIDE IS ONE of the most important crises with which practicing physicians must deal. There are a number of situations surrounding suicide which come to his attention. There is the case of the threatened suicide, the case of the suicide attempter who is seen (fortunately living) after a suicide attempt of greater or lesser severity has been made, and there is the situation of the family which has lost a member through suicide. These situations are crises not only for the victim and his family

but for the physician also. There are perhaps few situations which can arouse so much anxiety in a human being as that of suicide or suicidal activity in someone with whom he is involved.

Some idea of the frequency of this situation can be obtained by a glance at the statistics regarding suicide. For the last few years, the number of completed suicides in the United States has varied between 20,000 and 25,000 annually.<sup>1</sup> The average rate for this country is 10 per 100,000 population. Less adequate statistics are available for suicide attempts, since no way has been devised of accurately recording all of them. However, estimates based on clinical experience and some suicide census studies indicate that for every completed suicide, there are at least eight suicide

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The author is Associate Chief Psychiatrist, Suicide Prevention Center, and Associate Clinical Professor of Psychiatry, University of Southern California School of Medicine, Los Angeles.

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Reprint requests to: Suicide Prevention Center, 2521 West Pico Boulevard, Los Angeles, Ca. 90006 (Dr. Tabachnick).



attempts. Probably the number of persons who talk about suicide and think about it would include the majority of the entire population. Thus, the suicidal continuum of thought and activity is quite possibly a universal phenomenon.

Studies at the Los Angeles Suicide Prevention Center indicate that approximately 70 percent of people who die by suicide have consulted a physician sometime within the last six months of their lives. Although it is possible that many of them have managed to conceal their suicidal intention, this figure represents an important challenge for the physician. This is true because it is well known that the suicidal person is most often ambivalent: He wishes to die, but he wishes to live. The engaging of the wish to live with appropriate action to accomplish this end is *the* task in the treatment of suicidal ideation.

In addition to the actual number of suicide events, there is another most important issue associated with suicide. This is the sorrow, grief and depression generated in the people involved with the suicide attempter.<sup>2</sup> A treatment of suicidal situations has as its aim not only the preservation of life but the alleviation of emotional turmoil in troubled groups of people.

The observations and suggestions in this article are based on the following sources:

- Approximately 45,000 suicidal patients treated at the Los Angeles Suicide Prevention Center in the past ten years.
- A review of the values and shortcomings of treatments of suicidal situations by non-psychiatric physicians, psychiatrists and psychologists in the Los Angeles area in the past ten years.
- A review of over 2,000 cases of death in which "suicide," "probable suicide," or "possible suicide" has been listed as "cause of death."\*

## The Two Important Clinical Groups

Suicide is not a rigidly defined disease entity but rather a type of reaction which people approach through different routes. However, review of the statistics of suicidal personality characteristics, both in living and dead suicide attempters, indicates that a valuable clinical differentiation can be made between the previously mentioned two main types of suicidal individuals, the interpersonal group and the intrapersonal

group. As with all attempts to make broad generalizations about human beings, these classifications are not exact. The same variability of sign and symptom which can occur in any clinical syndrome holds true for suicide. It is also true that on infrequent occasions mixtures of these two types may be seen.

First, there are certain symptoms which are common to both groups. These include psychic depression, increased intake of alcoholic beverages and increased drug-taking.

### *The Interpersonal Group*

In the interpersonal suicide group of suicide activities, the following characteristics are present:

- There are frequently suicidal threats, suicidal actions (attempts), and other intimations of suicidal behavior which occur in interpersonal settings. For example, an individual in this group might make frequent references to death, might declare to relatives or friends that someone who has recently died is "better out of it," or might communicate to others that he is considering various ways by which a person might dispose of himself in a quick and easy way.
- There are often emotional outbursts, quick flashes of temper, anger and anguish expressed toward others.
- There is frequently a history of previous suicidal behavior, ideation, threats or attempts.
- The suicidal plan which members of this group possess is usually not well defined. Often there is no plan apart from the intention that if things continue to go badly, some kind of suicidal activity will take place.
- "Interpersonal attempters" often have clear and definite ideas as to how their crisis might be easily ended. They sometimes may be initially reticent about discussing their ideas. However, once this difficulty is penetrated and a bond of trust has been established, the thought as to what might terminate the emotional crisis is easily forthcoming.

An example of the interpersonal type of suicide activity follows:

A 23-year-old married woman with two young children was seen at a hospital following the ingestion of approximately twenty 0.1 gram Nembutal® capsules which resulted in a fairly deep coma. About nine months earlier she had come to Los Angeles from Kentucky with her husband

\*The cooperation of the Los Angeles County Coroner's Office under Drs. Currence and Noguchi is gratefully acknowledged.

who was pursuing the possibility of a good job. They were relatively recently married, and neither had been away from their hometown before. The patient considered herself a somewhat introverted person and found it difficult to find new interests and friends in Los Angeles. Indeed, her own choice would have been never to leave her hometown, but she had deferred to her husband's wish.

In the time they had been in Los Angeles, she had become moody and irritable, subject to frequent outbursts of temper with regard to her husband and had become increasingly fond of alcoholic beverages and sleeping pills. She said that she was not sure what was causing her tension. However, when the interviewer pointed to her loneliness and isolation since the move, she quickly admitted that she felt these factors were very important in her present condition.

Although she had thought about suicide on a number of occasions and had possibly communicated some suicidal ideas to her husband, she had no clearly formulated suicidal plan. However, on the evening of the attempt, following a moody introspective session in which she could feel no hope for the future, she impulsively swallowed the 20 capsules.

### *The Intrapersonal Group*

Specific symptoms in the intrapersonal group include:

- A progressive isolation from significant others and from valuable outside situations (such as job, church or club).
- The intrapersonal group differs decidedly from the interpersonal group in that the suicidal thoughts and activities are usually well concealed from others.
- Persons in this group tend to have well thought out suicidal plans and to have made preparations to implement them.
- They tend to be deeply depressed (as against the mild or moderate depression of the interpersonal group). They do not communicate their bad feelings, hopelessness and thoughts of suicide to others.
- They do not have available to them plans as to how their bad situation may be resolved (apart from suicide). One does not see quick "bounce-backs" from depression.

An example of this group is a 63-year-old single male. His close woman friend, after many weeks of urging, got him to go to the Suicide Prevention Center. At first he denied plans of suicide. However, he did indicate that he was increasingly depressed.

His difficulties seemed to have begun about ten years ago when his wife died. He took that loss very seriously and felt that he had never really recovered from it. Apparently during the depression that followed his wife's death his job performance decreased so that approximately two years after her death he lost the job that he had had for many years. He had drifted from one relatively non-skilled job to another, and usually each new job represented a step down. Recently, for long periods, he had been able to do no work at all and would spend a good deal of time in his cheap, one-room apartment, smoking and thinking.

He had had a woman friend for about a year, and at times they had been somewhat close. However, their relationship had recently begun to deteriorate. The friend did, however, think enough of him to try to get some help for him.

Only extremely active effort by a staff member induced him to continue his visits to the Suicide Prevention Center. Many times he would miss appointments, but usually after one or two calls he would come in again. He did manage to acknowledge that things were going very badly and that he thought of suicide and had a detailed suicide plan. However, it was very difficult for him to respond to the efforts of the staff member even though "all the stops were pulled out." After about two months of contact with the Center, he died in a fire that had apparently been caused when he fell asleep smoking a cigarette.

### **Treatment**

Various aspects of the psychotherapy of the two types of suicide attempters will be discussed here, and it should be said at the outset that one important adjunct to treatment that will not be commented on in detail is the pharmacotherapy of suicide, although drug therapy is a tool that should be considered in many cases. Some principles which should govern the prescription of drugs are these: They should be given symptomatically to deal with depressive and agitated symptoms of the patient. When they are prescribed to deal with these symptoms and are not conceived



of as a definite treatment for the suicide-producing situation, they can be most helpful. However, it must be kept in mind that drugs alone will almost never take care of the underlying dynamic situation that is producing suicide. Precisely because they can alleviate symptoms, they can be a two-edged tool. The physician must also seek to identify, either through his own investigation or by referral to a psychotherapist, the specific suicide-producing factors in each case. Such factors, once identified, must be diligently pursued. Only when drugs are used in an ancillary manner with this approach do they have a rational place in the treatment of suicidal conditions.

There are a number of causative factors for different suicidal situations. However, it is possible to make a general classification of factors which tend to move a person into suicide. This classification consists of (1) an external trauma or loss, and (2) an internal loss of hope.

Externally, the trauma or loss can take many forms. The most frequent precipitating factor for suicide is the loss of a valuable person. This loss can take place in many ways. The most common include death, divorce and lovers' quarrels. In addition to the loss of a significant other person, there can be other traumas to the individual. For example, his self-esteem can be wounded because someone he thinks highly of depreciates him. Likewise, his self-esteem can be adversely affected by not receiving a promotion at work or advancement at school. Loss of health and loss of financial assets are also often seen as precipitating factors.

At the same time that an external loss occurs, suicidal people undergo an internal loss. This is the loss of optimism, the loss of their feeling that it is possible for them to confront difficult situations, to judge what might be of value in regard to these situations, and then to implement such decisions.

An example of loss of self-esteem is noted in the case of the 63-year-old man cited earlier. At the time of his wife's death, he had been functioning quite well. However, the depression which followed her death brought on many feelings of loneliness, lack of enthusiasm for his job, and a consequent failure in effective work. The heavy drinking which he then indulged in only added to a vicious circle of loss of self-esteem, decrease in effectiveness, further loss of self-esteem.

In rare cases, the physician will observe only one of these factors (external or internal) to be operative. However, in the overwhelming majority of suicidal situations both kinds of loss are demonstrated. Indeed, the physician feels he is observing a complementary phenomenon. People undergo external loss at many times in their lives. In most instances, although they may feel somewhat disheartened by their loss, they are quickly able to summon up their resources and go ahead to some other form of activity which they feel has meaning and value. However, a certain proportion respond to loss with feelings that "life is just not worthwhile anymore."

The loss of hope can take a number of forms. Sometimes suicidal persons feel that the particular loss they have incurred is one that is irreplaceable. Therefore, it makes no sense for them to try to get anything else and to go on living. At other times, the feeling is more focused on the *abilities* of the suicidal person. Although he considers it conceivable that some lost object might be restored or replaced, he just does not feel that *he* could accomplish this. From this standpoint, suicide seems an attractive solution.

Even though extreme hopelessness is present at this time, it is important to keep in mind that almost all suicidal persons are ambivalent, that is, no matter how hopeless and interested in death they may be, there is an accompanying wish for life. This knowledge can provide the spark for the physician's effort to reach out to the suicidal person.

An important accompaniment of the feeling of hopelessness is the crisis situation that develops. Perhaps because the suicidal person does not think he can succeed, he makes no effort directed to planning and judgment.

Very often the suicidal person shows a breakdown of his ability to put first things first. For example, a person who admits that he is close to suicide and indicates that he would like to live may yet demur at going into the hospital on the grounds that he has to take his cleaning to the laundry. When it is recommended that he take some medication to counteract his depression, he will raise serious objections that the medication may be so overstimulating that he will not be able to perform his job, or that it will make him drive poorly and dangerously or forget to eat. He will



act impulsively, perhaps deserting his small children in order to seek solace in drinking or solitary driving.

Finally, he will be prepared to commit suicide when he undergoes some slight frustration, not realizing that once he is dead he will have no opportunity to pursue pleasures and responsibilities which are still of importance to him.

The treatment of suicidal situations, then, must be aimed at the two categories of etiologic situations. If there is loss of hope and disintegration of the personality, then therapy should be aimed at reintegrating the personality and restoring hope. If there is a loss of external valued objects, then attempts must be made to restore or replace them. What are the specific methods of accomplishing these ends?

### Reintegration of the Personality

An important keynote to the treatment of suicide is quick and decisive action. Most suicidal persons are in a state of turmoil which reflects their ambivalence about important issues in their lives. Should they stay with an unfaithful spouse, or should they leave? Can they afford to take a leave of absence from work or not? Indecision spreads from larger issues to smaller ones; for example, they may be plagued for hours by such trivial questions as what tie to wear.

In this situation, the quick recognition by the physician that a serious crisis exists and decisive action to implement improvement is of paramount value. Any point at which the physician senses that a suicidal crisis exists should become the starting point for quick action. He should request the patient to come in immediately and should be willing to make room in his schedule for dealing with this emergency.

Once the physician comes to a decision as to which actions will be therapeutic, he must act quickly to implement them. If he feels that a patient should go into a hospital, he must try to get the patient's consent immediately. Criteria for hospitalization include:

- A feeling of hopelessness that is not reversed during the initial interview with the patient. During this interview, the physician will have formulated a treatment plan. (For example, he may have decided that the patient should rejoin her parents, take an anti-depressant, and have regular psychotherapeutic interviews with him.) If the patient responds to the plan with a lifting of depression and

a feeling that things may indeed get better, this is a positive sign. However, if there is no improvement following the communication of the therapeutic plan, this points toward hospitalization.

- The presence of a psychotic state.
- A history of repeated impulsive suicide attempts while in a depressed condition.

On occasion, a patient for whom admittance to hospital seems clearly indicated will refuse to cooperate with such a procedure. What course should then be followed by the physician? If the patient's condition is such that he clearly seems to threaten his own life outside of a hospital, then steps for commitment can be quickly taken. Either a family member or friend or the physician himself may initiate such commitment procedures by getting in touch with the nearest psychiatric hospital or general hospital that has psychiatric in-patient facilities.

There are, however, a number of cases in which the issues will be ambiguous. The patient may not be clearly psychotic. Although the physician may feel that suicide is a strong possibility, the patient may not be talking about suicide at the time. On occasion, some suicidal patients will deny that they have suicidal intentions, but it will be felt that they are lying. Under such conditions, if commitment may not seem possible the physician will often have to settle for less than the ideal. He must inform the patient of his grave concern, offer him whatever seems helpful that the patient will accept, and tell him: "I want you to know that I want to help you and I am available at all times. If you should change your mind about entering the hospital, please feel free to call me." Although there are a few patients who may kill themselves under such conditions, such a sincere and open declaration of interest in the patient will (1) often sustain him and help him through the crisis, and (2) sometimes be responded to by a request for hospitalization.

Sometimes the physician will feel that admittance to hospital is not indicated, particularly if the suicidal patient can be brought close to someone who is interested in him. Such a person may be a family member, a friend, a member of the clergy or a sensitive paid helper such as a nurse. With suicidal patients, it is often necessary not only to make such suggestions but to go a long way toward seeing them effected. Thus a physician

may make a call to a patient's relative, discuss the seriousness of the patient's condition with him, and request the relative to take the patient to his home. Not only may such action be lifesaving, it will help restore to the patient the feeling that he is important—important enough to make someone take time and make significant effort on his behalf.

Once having made a diagnosis of the suicidal crisis, a non-psychiatrist may wish to refer the patient to a specialist in psychiatry or psychology. In some cases, however, this will not be possible, and in others it may be quite feasible for a physician with sympathetic human feelings to begin treatment himself.

In any case, whoever undertakes the crisis treatment and psychotherapy of the suicidal patient will have to deal with loss of hope in a person who is not capable of making sound decisions. The task here is to point out to the patient that certain of his decisions are not in his own best interest, and to point out how new decisions might be better than the ones he has come to. For example, the individual who feels that it is more important to go to the laundry than to a hospital where his life might be saved could have this poor judgment pointed out to him. It could then be stated that his life is more important than his laundry, and the suggestion in favor of the hospital could be made again.

Activities such as these will not only help the patient toward life-saving and more rational decisions but will also provide him with valuable models of thinking. A patient observing a therapist who has about him an air of "putting first things first" can see that such rational thinking is preferable to his own impulse-ridden thoughts and actions.

An additional tool in the therapeutic armamentarium should be the holding out of hope on the part of the therapist. This need not be done by explicit references to the fact that hope is necessary. The attitude of hopefulness is much more importantly conveyed by the therapist's attitude that the situation does have a good chance of resolving in a hopeful manner. Also the therapist should know, and he may wish to convey to the patient, that crisis and suicidal situations are most often short-lived, that they are periods of turmoil which pass away with time and with therapeutic effort, and as they do pass away, the patient emerges with restored hope.

Consider the following example. A 52-year-old woman called a physician because of concern that she would act on her suicidal feelings. These had begun after the death of her mother. The two women had lived together for many years with no other close contacts. Although the patient was a quite capable woman who had not only taken care of the home but had supported the couple through her employment, she felt hopeless and incompetent at the time she called, and wondered whether life was worth living.

The physician listened to her story, sympathized, and then pointed out that depression and despondency at such a time were quite normal, and that adjusting to the loss of her mother and finding new important relationships probably would take some time and involve a number of difficulties. However, he also pointed to her assets as exemplified by her past successes and the competence which had been present up to the time of her mother's death. The physician gave her his honest opinion that she would almost certainly be able to achieve a new adaptation as time went on. In the interim, he assured her, he would see her at weekly intervals, would give her an anti-depressant agent if necessary, and would be available for her to phone at any time.

The patient was mildly encouraged during the first interview and showed it by a decrease in depression. Over the course of the next three months, she manifested gradual improvement and at that time was able to discontinue medication and weekly interviews. For some months afterward, she called the physician on the average of once a month and then these calls stopped. A follow-up call a year later found the patient doing well.

The question has been raised, "Does conveying to the patient that the crisis situation is relatively short-lived contradict the dictum that quick and decisive action is called for?" This contradiction is more apparent than real. The point is that a feeling that the crisis will *eventually* be overcome must not take the place of instituting definite plans to help *implement* its being overcome. As a matter of fact, if the latter is not accomplished during the period in which the crisis is present, there may be an unfortunate successful suicide attempt.



## Restoration of Lost Objects

Next there is the issue of the restoration or replacement of the external objects. In the interpersonal group, this can often be fairly easily accomplished. Frequently a relationship which is deteriorating can be restored. A lovers' quarrel, an estrangement between two friends or relatives, can often be investigated for purposes of reconciliation, and often enough this possibility becomes an actuality.

In the case of the young wife whose history was described in earlier paragraphs, the following treatment ensued. When the husband learned of the cause for his wife's despair, he was overcome with guilt and was eager to do whatever would be possible to restore good and optimistic feelings in his wife. He readily agreed to return to their hometown, and a follow-up letter from the wife six months later revealed that things were going well.

Even in those situations where the specific lost individual cannot be restored, it is not too difficult to find substitute people or interests. Very often clergymen, business acquaintances or other friends of the suicidal, told of the patient's need for increased personal contact, will bring themselves closer to him. Sometimes they can be of great help by introducing the patient to new groups of people. We should not forget that many people welcome opportunity to be of help to others.

Nearly always the therapist willing to make the effort can find someone known to the patient who will agree to help in this friendly way. But if no one of that order can be found, it should be remembered that social workers, the Family Service, and the family groups of churches and certain social organizations are set up to help in such situations.

Also the possibility of the patient's reaching out for new interests and individuals should be actively explored. Attention should be paid to his own past history and his own personal predilection in the course of this attempt. Very often fraternal, school, church and social groups may be used in this endeavor.

In the intrapersonal group, the restoration of objects is much more difficult. This may be linked to the relatively less accessible approach to hope in these patients. However, by and large, the same means indicated to be useful in the interpersonal group should be attempted here.

One must expect, however, a much longer haul with intrapersonal suicidal patients. In this group, the therapist often becomes the new object. He must be prepared to enter into a long period of support and availability to his patient. He must recognize that although many patients will respond to this kind of therapy, the response may not be an easy or quick one. Such patients often become extremely onerous for internists, general practitioners or others who do not have the specific resources that trained psychotherapists have. However, should there be a feeling of particular interest or liking for such a patient on the part of a non-psychiatrist physician, there would be no contraindication to his undertaking such a therapy.

Some may question that a person who is not psychiatrically trained could effectively treat a severely disturbed long-term patient. However, experience indicates that the qualification of genuinely caring for another person is perhaps the single most important condition in treating suicidal patients. Such a feeling of caring is probably more important in many cases than years of specialized training.

Certain suicidal situations demonstrate that the ministrations of a good friend can get someone through an extremely lethal suicidal situation. We have had an opportunity to utilize lay volunteers at the Suicide Prevention Center for many years. These people have come to the Center because of a feeling of wanting to help others, and they are accepted as workers when it is felt that they can effectively act on this motivation. This group has been consistently successful in dealing with suicidal situations, including many of the serious intrapersonal ones.

Of course, it is valuable to utilize the services of a consultant. Consultation is important even in the most highly skilled psychiatric treatment of a suicidal patient, and it is at least equally important in psychotherapy performed by persons who are not so highly trained.

In all suicidal situations, attention should be paid to the persons who are in one way or another near to or associated with the suicidal attempter. As already indicated, these significant others are often quite crucial in the treatment of suicide. In the first place they are important because it is often due to rifts or difficulties with them that the suicidal ideation is set into motion. Further, as already has been indicated, enlisting the support of the family



and those around the patient can often be of extreme help to him. It should be mentioned that the physician is not confining help to the suicidal victim when he is engaged in such collaborative work. Very frequently, the person who makes the suicide attempt is only the most obviously disturbed member of a group of people who are undergoing symbiotic problems. Often the suicide attempt of one member is the alerting signal by which an entire constellation of disturbed interpersonal relationships is brought to attention.

An example of the suicide attempter being the disturbed individual in a family group is the following:

A young man made a serious suicide attempt and because of it was admitted to hospital. At first he was reticent to talk about his condition but after some indication of interest on the part of the interviewer, the following story emerged.

He was in love with a girl whose background was unacceptable to his parents. Over the course of a year, the mother repeatedly told him that his marrying the girl would be extremely distasteful to her. Because of his great dependency on his family, this threw him into increasing turmoil which finally culminated in the suicide attempt.

In an ensuing interview with his mother, it became apparent that there was more to the matter than her dislike of the particular girl. Her own marriage was unsatisfactory to her, and she had only been able to maintain her sense of well-being by pouring all of her energy into the relationship with her son. The threat of his leaving her through marriage brought about increasing anxiety and thoughts of suicide. These concerns were important in her attitude toward her son.

It is obvious that in this situation, therapy had to be directed to mother and son, and eventually to the father also. (The latter was necessary in order to help bring together the mother and father so that the mother could relinquish the need for her son.)

## The Family and Friends of Suicides

Next we will consider those unfortunate situations in which a suicide has actually taken place. Those surrounding the person who has killed him-

self will often feel responsible and guilty for the death. They must be reassured. They need the support of a philosophy of life which indicates that no person is omnipotent. They should be informed that, much though we may care for another person, there are forces that are greater than our own efforts which may act to make that person take his life. They must be reassured that their irritation and anger toward the dead person were not damnable sins but rather human reactions. Although it is natural that they should feel a sense of sorrow and loss, in most cases it is not appropriate for them to take the responsibility for the death upon their own shoulders.

Finally, a word should be said about the children of suicide victims, who not only have to live with the loss of one of the two most important people in their early lives, but also are left with the necessity to deal with the frustration and anger that may accompany such a loss. Although some persons might think that to feel angry toward someone who is so troubled as to kill himself is irrational (and perhaps it is), such feelings are also quite natural. A close watch should be made of surviving children so as to quickly identify indications of emotional turmoil. Such turmoil may manifest itself through any of the indications of psychological distress (anxiety, depression, psychosomatic symptoms, hypochondriasis, dissociative states, psychotic states). The point is that a suicide of a parent may often predispose a child to emotional turmoil in later life.

*Author's note:* A number of additional articles may be consulted by the clinician interested in treatment of suicidal conditions. These include: "Acutely Suicidal Patients" by Robert E. Litman, *CALIFORNIA MEDICINE*, 104: 168-174, March 1966; "Some Practical Procedures in the Management of Suicidal Persons" by Ronald S. Mintz, *American Journal of Orthopsychiatry*, 5:896-903, October 1966; and "The Suicidal Patient and the Physician" by Norman L. Farberow, Edwin S. Shneidman, and Robert E. Litman, *Mind*, 1:69-74, March 1963. An article which gives additional helpful material is "The Practical Management of Depression" by Nathan S. Kline, *JAMA*, 190:732-740, November 1964.

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# Nonspecific Urethritis in Females

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■ *The possibility of nonspecific urethritis must be considered in females with persistent irritative symptoms of the lower urinary tract despite "negative" urine cultures. The diagnosis can be made only by the proper collections of urine specimens from both the urethra and the bladder. These specimens will reveal the presence of white blood cells in the urethral washings, while the midstream (bladder) specimen will be free of cells.*

NONSPECIFIC URETHRITIS in males is frequently manifested by a watery urethral discharge, causing spotting of underwear or bedclothes. It is usually associated with mild irritative symptoms of the lower urinary tract. Men are instantly aware of a problem and are very quick to seek medical attention for this emotion-laden area of the body.

The causative organism, which is thought to be a pleuropneumonia-like organism (*Mycoplasma*) is not seen under ordinary light microscopy, nor can it be identified by the usual culture techniques. If a frank urethral discharge is not present, the urethral washings ("first glass") specimen typically reveals white blood cells but no organisms, while the midstream ("second glass") specimen may have no evidence of cells. It is, therefore, only by examination of both the first glass and midstream specimens that the diagnosis of this entity which we call "nonspecific urethritis" can be made.

A similar entity can occur in females. However, the physician in his high regard for sterile, uncontaminated specimens, usually obtains only a

clean-voided midstream or catheter specimen. Hence a woman with persistent symptoms of the lower urinary tract irritation yet with clear urine specimens from the bladder, is all too often considered to have psychological problems, the urethral washings going unnoticed. But in females as in males, the diagnosis of "nonspecific urethritis" is made by establishing the presence of white blood cells in the urethral washings, while the midstream specimen is free of cells. The clinical problem usually clears rapidly with the use of tetracycline.

## Reports of Cases

*Case 1.* A 22-year-old unmarried nurse had a one-month history of symptoms of the lower urinary tract irritation and terminal hematuria. She had been treated by her physician with both sulfonamide and nitrofurantoin, but the symptoms persisted. A catheterized urine specimen was free of cells and bacteria, both microscopically and on routine and acid-fast bacilli culture media. Neither excretory urograms nor endoscopic examination revealed any gross abnormalities. Reflux was not seen on voiding cystourethrogram. A course of urethral dilations gave no relief.

Two-glass urine specimens were obtained after medications had been discontinued for one week.

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The first glass specimen revealed white blood cells with no bacteria either on culture or methylene blue stain. The midstream (second glass) specimen was essentially clear. Following a course of tetracycline, the symptoms as well as the urethral washings cleared completely. One recurrence three months later responded similarly to tetracycline.

**Case 2.** A 34-year-old physician's wife, para 6, gravida 6, had a history of recurrent episodes of urinary tract infection over a period of five years. They had usually responded promptly to sulfonamide. Over the previous six weeks, however, she had been treated with sulfonamide, nitrofurantoin and ampicillin without abatement of the irritative symptoms. Work-up, including excretory urograms, cystoscopy and voiding cystourethrography, failed to reveal any cause for the problem. Urethral washings showed 4 to 5 white blood cells per high power field, with midstream urine free of cells or bacteria. Urine specimens obtained after a two-week period of no medications showed no growth on eosin-methylene-blue stain (EMB), blood agar, or Mueller-Hinton media. Following a course of tetracycline, symptoms abated and there were no longer cells in the urine.

## Discussion

The male anatomy permits easy and accurate collections of urethral and midstream specimens. For comparable collections from females, proper perineal preparation must be carried out.<sup>1,2</sup> Our office nurse carefully cleanses the patient's periurethral and intralabial areas and plugs the vagina with cotton. The patient is then instructed to void into two separate sterile containers, finishing the final voiding in the toilet. Both specimens are then plated out on blood agar, EMB, and Mueller-Hinton media. When possible, attempt is made to isolate the mycoplasma organism.<sup>3</sup>

The evidence suggests that the offending organism is the T-strain *Mycoplasma*,<sup>3-7</sup> although

Ingham and associates<sup>8</sup> question whether the incidence of this organism is, indeed, statistically higher in patients with clinical urethritis than in a "control" group. There is little doubt that all of the studies indicate we are dealing with a distinct clinical entity, characterized by the symptoms and laboratory findings outlined above. The condition appears to be venereal in nature, which is suggested by the high recurrence rate following repeated sexual contacts.<sup>9</sup> The findings similarly suggest that either the male or the female may act as a carrier and hence that treatment of both sexual partners is advisable.

Although there is still question as to the particular offending organism in "nonspecific urethritis," the clinical problem usually clears rapidly with the use of tetracycline.<sup>10</sup> It is not within the scope of this paper to define the causal agent for the condition which we refer to as "nonspecific urethritis," but rather to try to make the clinician aware of its possible presence in the female with persistent symptoms of lower urinary tract irritations but negative cultures. Only by properly collected urethral and bladder specimens can the condition be recognized.

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# The Normal Thyroidal Uptake of Iodine

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■ *The range of values for the 24-hour thyroidal accumulation of radioactive iodine in euthyroid persons varies with geographic location. In the San Bernardino Valley region of Southern California the "normal range" is 6 percent to 33 percent in euthyroid subjects. This is lower than in studies from other areas of the United States. The urinary iodide excretion and the absolute iodine uptake of the thyroid are higher than in studies from many other areas of the United States, pointing to iodine abundance as the reason for this difference. The geographic variation and the possibility of changing dietary iodine intake of normal persons point to the necessity of current and local determinations of the "normal range" of the thyroidal uptake of radioiodine if the results of this thyroid function test are to be properly interpreted.*

THE THYROIDAL UPTAKE of radioactive iodine in persons without thyroid disease varies with geographic location,<sup>1-5</sup> and may change in the same location from one decade to the next.<sup>6</sup> With the opening of the new Loma Linda University Hospital in Loma Linda, which is in the San Bernardino Valley region of California, it became apparent that the 24-hour thyroidal uptake of I<sup>131</sup> in our patients without thyroid disease did not correspond with the usual "normal ranges" of 20 to 50 percent or 15 to 45 percent.<sup>7</sup> Accordingly, a study of the range of radioactive iodine uptakes in euthyroid subjects was undertaken.

## Methods and Materials

Three hundred twenty-eight 24-hour I<sup>131</sup> thyroidal uptake determinations were performed from

February 15 to May 14, 1968, in the Section of Nuclear Medicine. Forty were performed in patients who had received medications or who had non-thyroidal conditions which might alter the thyroidal uptake of iodine including exogenous iodides,<sup>8</sup> thyroid hormones,<sup>9-13</sup> adrenal steroids,<sup>14-16</sup> ACTH,<sup>14-16</sup> phenylbutazone,<sup>17</sup> para-aminosalicylic acid,<sup>17</sup> thioureas,<sup>18</sup> infancy,<sup>19</sup> pregnancy,<sup>20,21</sup> congestive heart failure,<sup>22,23</sup> renal disease,<sup>23,24</sup> and hepatic failure.<sup>25</sup> Thirty-six uptake determinations were performed following thyroidal stimulation or thyroidal suppression. There remained 252 determinations in 244 patients. Where repeat studies were performed on a single patient the initial I<sup>131</sup> uptake was used in this study.

A conclusion regarding the thyroidal status of 236 of these 244 patients could be reached on the basis of the total clinical and laboratory evaluation of the patient, including examination by the authors. Eight patients were excluded because the thyroidal status remained uncertain. One hundred and four of the 236 patients had thyroid disease.

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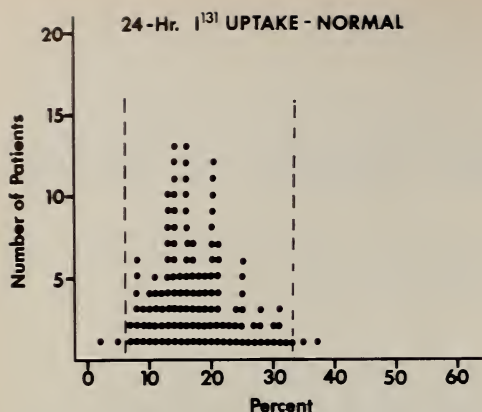


Chart 1.—Range of  $I^{131}$  uptake as determined in euthyroid subjects in San Bernardino Valley region of California.

The other 132 patients were free of thyroid disease, had received no interfering medication and did not have non-thyroidal conditions known to alter the thyroidal uptake of radioactive iodine. Thirteen of these subjects were apparently healthy hospital personnel who served as volunteer control subjects. The values for the 24-hour  $I^{131}$  uptake in these 13 volunteers did not differ significantly from the values in the 129 euthyroid patients as determined by the T-test, therefore, these two groups were combined and constitute the subjects on which this report is based. Radioactive iodine uptakes were performed with an average tracer dose of 10  $\mu$ c. Measurements were taken at a distance of 35 cm from the crystal. Tissue background was counted over the thigh. The standard was measured in an ORINS thyroid phantom at the most superficial level. Urine  $I^{131}$  was counted in a conventional well counter. Urinary iodine was determined from appropriately diluted aliquots of urine by the commercial method of Hycel, Inc.<sup>26</sup> The absolute iodine uptake (AIU) of the thyroid was calculated from 24-hour measurements by the formula of Alexander et al,<sup>27</sup>

$$AIU = \frac{I^{131} \text{ uptake} \times \text{urinary iodine}}{\text{urinary } I^{131}}$$

while the subjects were on random diets.

## Results

The values of the 24-hour thyroidal  $I^{131}$  uptakes are shown in Chart 1. They range from 2 percent to 37 percent with a mean of 17.6 percent. These

values do not conform to a normal curve of distribution. The failure of the thyroidal radioactive iodine uptakes of euthyroid subjects to follow a normal distribution curve has been reported by others<sup>27,28</sup> and may be due to the practice of including patients of various ages and both sexes in a single group even though these factors have been shown to influence the thyroidal radioiodine uptake.<sup>29-37</sup> Using the statistical tests for skewness and kurtosis, the transformation of our data which best fit the normal curve of distribution was the square root of the radioiodine uptake. Therefore, the square of the mean square root plus or minus two standard deviations from the mean square root ( $4.11 \pm 1.61$ )<sup>2</sup> was chosen as our "normal range." This range is from 6 percent to 33 percent in 24 hours. Twenty-four hour urinary iodine excretions were measured in ten of the apparently healthy volunteers and ranged from 179 mg to 535 mg with a mean  $303 \pm 41$  mg in 24 hours.\* The mean AIU of these volunteers was  $4.0 \pm 0.9$  micrograms per hour or 96 micrograms per 24 hours.

## Discussion

In Jamaica normal persons have 24-hour thyroidal radioiodine uptake of 0 to 36 percent and 61 percent have values below 10 percent.<sup>2</sup> This is in contrast to the range of 30 percent to 70 percent for euthyroid persons in Denmark.<sup>1</sup> Within the United States, the "normal range" has been reported to be as low as 6 percent to 32 percent in Gainesville, Florida,<sup>3</sup> and as high as 20 percent to 50 percent in New York<sup>4</sup> and New England.<sup>7</sup> Other investigators in the United States report values between these two extremes.<sup>11,38-52</sup> There is evidence that higher ambient temperatures are associated with lower radioiodine uptakes,<sup>53</sup> though not all studies are in agreement.<sup>37</sup> The importance of this factor in our subjects is unknown. Dietary iodine intake is important since the radioiodine uptake reflects both thyroidal iodide accumulation and the amount of stable iodide in the body with which the radioiodine trace is diluted.<sup>5,27,54,55</sup> Iodine deprivation will elevate the radioactive iodine uptake in euthyroid persons<sup>8,17,52</sup> and radioiodine uptake is higher in regions of iodine deficiency even in the absence of goiter.<sup>56,57</sup> Conversely, the feeding of iodine and abundant dietary

\*Mean  $\pm$  S. E.



iodine intake are associated with lower radioiodine uptake.<sup>5,8,55</sup>

The mean 24-hour urinary iodine excretion of 303 micrograms per 24 hours in the euthyroid subjects in this study is higher than the 91 micrograms per 24 hours reported by Koutras and co-workers for euthyroid subjects in Glasgow,<sup>54</sup> the 100-200 micrograms per 24 hours reported by Means et al for euthyroid subjects in New England<sup>7</sup> or the 240 micrograms per 24 hours reported in euthyroid subjects in San Francisco by Reilly et al.<sup>11</sup> It is similar to the 301 micrograms per 24 hours in euthyroid subjects in Arkansas.<sup>58</sup> The AIU has been reported to be 2.3, 2.7, 2.9, and 3.7 micrograms per hour<sup>27,54,59,60</sup> or 70, 82, and 85 micrograms per 24 hours<sup>11,58,59</sup> in euthyroid subjects in Scotland, France, Canada, and the United States. The mean of 4.0 micrograms per hour (96 micrograms in 24 hours) found in this study is higher than in other studies reported in the United States but below the 6.2 micrograms per hour reported by Nagataki in normal Japanese whose dietary iodine intake is very high and whose mean 24-hour thyroidal I<sup>131</sup> uptake is 14 percent compared with 17.6 percent in the present study.<sup>55</sup> In normal subjects urinary iodine is inorganic iodide<sup>61</sup> and the renal clearance of iodide remains constant with variations of the plasma inorganic iodide level.<sup>61</sup> Therefore, the higher urinary iodine excretion in our euthyroid subjects reflects a higher plasma inorganic iodide level. An elevation of the plasma inorganic iodide, AIU, and urinary iodine excretion follows increased iodine intake.<sup>27,55,59,62,63</sup> These data point to an increased iodine intake and consequent stable iodine dilution of the radioactive iodine trace as the reason for the relatively low 24-hour I<sup>131</sup> uptake in euthyroid subjects in this region of California.

Difference in geographic location may not be the only factor in the difference between the results of this study and those reported from other areas. In a recent study from Alabama, Pittman, Dailey and Besch<sup>6</sup> showed that the mean normal 24-hour thyroidal radioiodine uptake decreased in that area from 28.6 percent to 15.4 percent during the preceding decade, largely as a consequence of the increasing iodine content of bread resulting from newer baking methods. The normal values may be falling in many areas of the United States and in the past may have been higher in and about Loma Linda, the region of the present report.

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## ALCOHOL AND LARYNGEAL CANCER

"There has been much less publicity about the connection between alcohol and cancer than there has been about smoking and cancer. I think the alcohol lobby must be even more effective than the tobacco lobby. . .

"[But statistics tell the tale.] Out of the several hundred people I have seen with cancer of the larynx, there were four non-smokers. Out of the several hundred people I have seen with cancer of the pharyngeal mucosa . . ., there were three non-alcoholics. A significant number of people who have carcinoma in the larynx are heavy drinkers and heavy smokers. Perhaps you think that alcohol doesn't get to the vocal cords when you swallow. Actually, not everything is blocked off at the false cord level. . . . Why do you think there is the so-called whisky voice? Why do you think people's voices are a little bit hoarse and raspy the morning after a big cocktail party — too much smoking, too much drinking, and too much talking loudly over the noise of the cocktail party. We feel that the drinking is an important part of it. . . .

"You can't turn this around and say everybody who smokes and drinks is going to get cancer. The trouble is that you can't tell ahead of time whose mucosa is going to be sensitive to these things and whose isn't."

—HERBERT H. DEDO, M.D., San Francisco

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# CASE REPORTS

## Rocky Mountain Spotted Fever In Monterey County, California

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ROCKY MOUNTAIN spotted fever is a rickettsial disease which is widely distributed throughout North America. Signs and symptoms of this disease were recently reviewed.<sup>1</sup> The purpose of this paper is to report the first known case of this disease from Monterey County, California, and to add an additional consideration to the differential diagnosis in a patient from this area who presents with fever and a rash.

### Report of a Case

A 25-year-old white man was in good health until, two days before admission, fever and chills developed.

He had not traveled outside California for several months and for at least three weeks before admission had not been out of the Fort Ord area. He had received typhus immunizations approximately 12 weeks before the present illness.

On physical examination the patient appeared to be acutely ill. The temperature was 38.9°C (102°F), the pulse rate 96 and blood pressure 122/80 mm of mercury. There were bilateral conjunctival petechiae. A large number of macules, some of them petechial, were scattered over the trunk and extremities but not on the palms and

soles. The liver and spleen were of normal size and meningismus was not present.

A clinical diagnosis of meningococcemia was made and, before therapy was begun, blood cell count, urinalysis, aerobic and anaerobic blood cultures, spinal fluid examination, determination of blood urea nitrogen and fasting blood sugar were carried out and a Gram stain of material from petechiae was prepared. Blood was drawn and frozen for serologic studies. Therapy was begun with 5 million units of aqueous penicillin intravenously and aspirin by mouth. The petechial smear was said to be positive for Gram-negative diplococci. The leukocyte count was 6,600 per cu mm with 53 percent neutrophils, 28 percent banded forms and 19 percent lymphocytes. Platelets were estimated to be normal and remained so throughout the stay in hospital. Spinal fluid, blood cultures, urinalysis, chest roentgenogram, fasting blood sugar, blood urea nitrogen, heterophile agglutination, and cold agglutinins were all negative or normal. Liver function studies on the eighth hospital day were normal with the exception of mildly elevated serum glutamic oxaloacetic transaminase.

During the first three days in hospital, the rash became more petechial and a few lesions were noted on the soles of the feet. The leukocyte count decreased to 2,100 per cu mm. The temperature continued at 38.9 to 40°C (102-104°F) and the patient complained of headache. As the course was atypical for meningococcemia, the patient was again interviewed and it was found that about 7 to 10 days before admission, while on bivouac, the patient had found a tick crawling on him, but there was no clear-cut history of tick bite. In light of the highly suggestive history and the clinical course of illness, however, penicillin was discontinued and tetracycline was begun on the seventh hospital day. The patient became afebrile within 24 hours and made uneventful recovery.

Rickettsial complement-fixation studies disclosed the following: *Rickettsia rickettsii* on March 3 was less than 1:5; March 18, 1:40; April 2, 1:80; and studies for typhus showed titres of 1:10, 1:40,

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1:20. A Weil-Felix test during the second week of illness was "positive" at 1:320, *Proteus* OX-19, but this was considered unreliable due to recent typhus immunization.

### Discussion

In retrospect the foregoing case is rather classical for Rocky Mountain spotted fever. However, the rare occurrence of this disease in this area of California, a "positive" petechial smear, and a relatively large number of cases of meningococemia occurring at the time caused a delay in diagnosis. In a review of the reportable disease records of the California State Health Department back to

1927, no reports of this disease from Monterey County were found.<sup>2</sup>

At present a survey of the tick infestation is being done at Fort Ord Army Reservation to determine the presence of a vector and whether the vector harbors the organism.

The diagnosis of Rocky Mountain spotted fever should be entertained in the febrile patient with a rash which is or becomes petechial.

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### HOUSE DUST ALLERGY

"Injection treatment has no place in house dust allergy unless it's preceded by attempts to get rid of the house dust, especially in the bedroom. Nearly half a person's life may be spent in that room. Eighty percent of the child's exposure to house dust occurs in his bedroom. . . . The sources are kapok and cotton lintens, mattresses and box springs, stuffed toys and upholstered furniture, and rugs and rug pads. . . .

"Anyone with house dust allergy should never have a feather pillow — that's asking for trouble. If he's not allergic to feathers, he shouldn't try to become allergic by exposing himself. There should be allergen-proof casings on the box springs and mattress, and in the case of children, no stuffed toys. There should be no upholstered furniture. Written directions for house dust control should be given the patient along with order blanks for the encasings. I tell the patient that he may have any non-wool rug, any non-animal epidermal rug (cotton, rayon, or nylon is fine). He can have a rubber rug pad, no pad, any pad except a cow-hair pad."

—WILLIAM C. DEAMER, M.D., San Francisco  
Extracted from *Audio-Digest Otorhinolaryngology*, Vol. 2, No. 12, in the Audio-Digest Foundation's subscription series of tape-recorded programs.



## Balantidium Coli Infection In a Vietnam Returnee

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DIARRHEAL DISEASES are common in American troops in and returning from Southeast Asia. Most cases are bacterial, usually due to *Salmonella* or *Shigella* organisms. Protozoal infections, especially amebiasis and giardiasis, are also commonly seen. Balantidiasis, on the other hand, is rarely seen and therefore less likely to be considered in the evaluation of patients with diarrhea.

### Report of a Case

A 19-year-old Caucasian man was admitted to Tripler General Hospital in May 1969 with chief complaint of diarrhea. A month before admission he noted nausea and he vomited once. Shortly afterward watery, brown, often explosive diarrhea developed, defecation occurring four to six times a day. This persisted and was associated with anorexia and an 8 or 10 pound loss in weight. The patient had been stationed in the Republic of Vietnam for nine months and had occasionally drunk well water. Three months before admission he was treated for hookworm infection. He denied fever, fatty stools, melena or bright red blood per rectum. Past medical history was unremarkable.

When examined he was observed to be thin, well-developed and in mild distress. Explosive diarrhea was occurring every 20 minutes when he

was first seen. Blood pressure was 108/68 mm of mercury, pulse rate 78 per minute and temperature 37.5°C (99.4°F).

Bowel sounds were hyperactive and there was tenderness in the upper and lower left quadrants of the abdomen. No hepatosplenomegaly was present. No abnormality was noted in the remainder of the examination.

Leukocytes numbered 10,300 per cu mm with a normal differential. Platelets appeared normal on the blood smear. The hematocrit was 44 percent and hemoglobin content was 15.8 grams per 100 ml. On microscopic examination of a fresh stool specimen many large, oval, ciliated parasites with an easily definable macronucleus and several small vacuoles characteristic of *Balantidium coli* were seen. Results of other studies, including stool cultures and liver function tests, were negative or within normal limits.

Following the diagnosis of balantidiasis, the patient was treated with tetracycline 250 mg four times a day and Diodoquin® 650 mg three times a day for 21 days. He became asymptomatic within 36 hours and no abnormalities were noted in subsequent stool examinations.

### Comment

*Balantidium coli* is an oval, ciliated, actively motile protozoan, measuring 50 to 75 micra in length. It contains a large, kidney-shaped macronucleus and usually two contractile vacuoles. A micronucleus may be found near the concavity of the macronucleus. The constantly moving cilia are visible under high-power magnification. It infects man incidentally, the hog being the usual definitive host.<sup>1</sup> The disease is uncommon and has not been frequently reported in the American literature.<sup>2</sup> In one large study of 3,600 patients with diarrheal diseases, the incidence of *Balantidium coli* was only 0.44 percent.<sup>3</sup> The low incidence of infection and failure to transmit the disease experimentally suggests that man has a high resistance.

The severity of symptoms with *B. coli* varies. Some patients are asymptomatic, but in the majority diarrhea is characteristic, with as many as 5 to 25 stools per day.<sup>1</sup> On occasion, severe dysentery may be noted, with liquid feces containing mucus, blood and pus. Tenesmus, colic and tenderness over the colon are also present.

Diagnosis depends on demonstration of trophozoites in a diarrheal stool. The large size of the parasite, its constant ciliated movement and large

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nucleus permit easy identification of the organism.<sup>4</sup> Treatment with Diodoquin® and tetracycline is safe and effective and probably represents the preferable mode of therapy,<sup>4</sup> although ampicillin may be equally effective.<sup>5</sup>

The possibility of balantidiasis should be considered in evaluating patients with diarrhea who have been in Southeast Asia.

#### TRADE AND GENERIC NAMES OF DRUGS

*Diodoquin*® . . . . . 5,7-diiodo-8-hydroxyquinoline

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#### THE "PRIVATE PRACTICE" AMPICILLIN RASH

"Rubella-like rashes are quite common after ampicillin. It's of interest that these are rarely seen in hospitals and they are commonly seen by practicing physicians and outpatient departments. If one breaks this down, it appears that the rashes are more commonly seen if the drug is given orally than if it is given intramuscularly and that the highest incidence appears in patients who receive ampicillin orally for respiratory infections. This puzzled us for a while; but I think the answer is probably at hand.

"A number of months ago, an article in the British journal *Lancet* indicated that if a patient with infectious mononucleosis received ampicillin, . . . he would invariably get a rash—either an ampicillin or an infectious mononucleosis rash. We therefore gave our next few infectious mononucleosis patients ampicillin and sure enough within 24 hours they had a rash. In children whose heterophil determinations are quite unreliable, this turned out to be a pretty good test for infectious mononucleosis.

"This suggested that the reason rubella-like rashes occur in respiratory disease is because most of these diseases are viral, much like infectious mononucleosis. What the patient has before he gets the ampicillin is a mild, transient involvement of his blood vessels, a very mild vasculitis which is quite common with viral infections. When you add ampicillin, which can also produce a mild vasculitis, the patient gets a rash. This would be a very fine explanation of why it is so commonly seen in private practice where the drug is used for the treatment of respiratory disease and so rarely in the hospital where it is used primarily for the treatment of such obvious bacterial conditions as meningitis and shigellosis."

—HEINZ F. EICHENWALD, M.D., Dallas

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# The Nature and Treatment Of Stress Ulcers

## A Review

CARL B. NAGEL, M.D., *Irvine*

STRESS ULCERATION of the gastrointestinal tract was recorded by the ancients. Twenty centuries ago Celsus observed this phenomenon in men suffering the extraordinary tensions of a rigorous military campaign. No doubt it has been with us from the very start of man's indulgence in warfare. As we have shown no particular inclination to give up this aspect of human activity, one may predict stress ulcers will remain with us for the foreseeable future. While war may represent the ultimate in stress, the life of the civilian is hardly without great tension. The extreme physiologic agitation which may lead to ulceration in a combat soldier finds its parallel in the stresses and strains of a major operation or in local or systemic disease processes of unusual virulence and magnitude.

### Definitions and Nomenclature

In medicine, as in virtually all science, definition often takes the form of classification. Medical classification is based upon clinical behavior, on morphologic appearance or on known or implied etiologic factors. Those who do the classifying use one or the other of two fundamentally very different approaches. There are the lumpers and the splitters. The lumpers tend to put many or all examples of a certain problem into the same cate-

gory and sometimes a single word or apt phrase may be found or coined to identify and accurately represent the whole problem. The splitters earn that epithet: As soon as a species (in natural history, for example) is defined, they gleefully go about discovering and describing more or less numerous subspecies. (One need but think for a moment of the species man—*Homo sapiens*—to recognize in himself the natural tendency toward lumping or splitting.) It is difficult to say which approach, when diligently pursued and translated into therapeutic action, comes closest to the truth. Stress ulcer is a wonderful example of this very thorny problem. If it could be simply defined, perhaps it could be simply or at least uniformly treated with a higher degree of success. Unfortunately, this little corner of utopia is not yet well mapped. Even in attempts to define the word *stress*, the problem becomes almost impossibly complex. There are knowns as well as unknowns, however, and it is upon these that attention should be focused.

### Pathologic Anatomy

If one word could be used to describe the appearance of a stress ulcer under the microscope, that word would be *acute*. Figure 1 illustrates a typical example. The ulcer penetrates deeply but there is little or no evidence of fibrosis (chronicity). Much fibrin and numbers of acute inflam-

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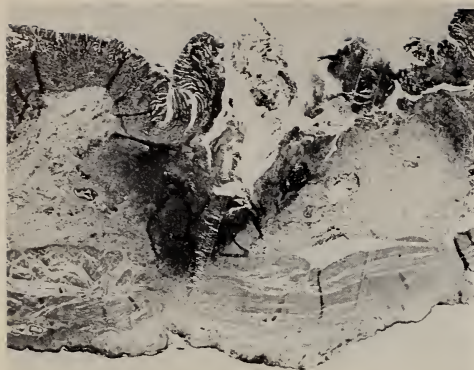


Figure 1.—Photomicrograph showing a typical stress ulcer ( $\times 10$ ). There is evidence of acute inflammation but no fibrosis.

matory cells frequently are present. The borders between the ulcerated region and the adjacent mucosa are often surprisingly sharp, but other areas of the involved organ may show changes which possibly represent the beginnings of a second ulcer or erosion (Figure 2). Very pronounced vascular congestion is the striking feature of the latter lesions. It is not difficult to imagine that dissolution of the surface mucosa is the next step (Figure 2).

The anatomic location of such ulcers is of great clinical importance. The widely held impression that stress ulcers are always numerous and have a tendency to involve the entire organ is not sustained by the facts.<sup>1,2</sup> Table 1 is a summary view of our own autopsy material over the past five years. When multiple ulcers were present, they tended to appear as satellites grouped about a larger and apparently primary lesion. Hence, although two to five or more ulcers were present in a number of cases, large portions of the involved organ still were spared. When multiple gastric ulcers did occur, they were located in the antrum or antrum and lower body in two-thirds of our cases. When combined with duodenal lesions, the ulcers were always antral in location.

TABLE 1.—*Relative Incidence of Single and Multiple Stress Ulcers as Noted in Autopsy Material in a Five-Year Period*

Single gastric	8
Single duodenal	9
Multiple gastric	25
Multiple duodenal	7
Combined gastric and duodenal	9



Figure 2.—Photomicrograph illustrating massive vascular congestion at the mucosal surface, perhaps the early stage of an oncoming frank ulceration ( $\times 100$ ).

Curling's original report<sup>3</sup> described only duodenal lesions occurring in association with burns. Several of Cushing's patients also died of duodenal rather than gastric lesions.<sup>4</sup>

Reports in the literature<sup>5,6</sup> show about 30 percent of stress ulcers are duodenal, with gastric or combined gastro-duodenal ulcers accounting for most of the remainder.

Acute ulcers of the esophagus, jejunum, and colon also have been described.<sup>4,7,8</sup> The small and large bowel lesions appear to be agonal, but the reports of esophageal lesions are more difficult to interpret.<sup>4,8</sup> A beautiful drawing of a huge perforated esophageal ulcer appears in Cushing's classic article.<sup>4</sup> Cushing considered esophageal involvement as part of the same overall process. In our own necropsy series, 7 of 58 patients had esophageal ulcers or erosions, some of which had perforated, death quickly following. In each of the patients with esophageal ulcers violent and prolonged retching and vomiting, whatever the cause, dominated the clinical manifestations. The implication that these lesions were the result of such vomiting or retching or both is clear.

TABLE 2.—Diseases Associated with Acute Peptic Ulcer  
(51 Autopsy Cases—UC Irvine Series)

Cases	Ulcer		
	Primary Cause of Death	Contributing Cause of Death	Agonal only
12 Central nervous system . . . . .	6	4	2
12 Malignant tumors . . . . .	7	2	3
7 Infections . . . . .	4	2	1
9 Cardio-respiratory disease . . . . .	4	4	1
4 Renal failure . . . . .	1	1	2
6 Liver disease . . . . .	5	0	1
1 Amyloidosis . . . . .	0	1	0

## Etiology

The exact cause of stress ulceration, at least as expressed in precise and unequivocal terms, is unknown. A strong case for guilt by association can be made, however. The associations are varied almost without limit. The stress, whatever it may be, is always extraordinarily severe. If it be a thermal burn, the burn is extensive or complicated.<sup>6,9,10,11</sup> If it be operation, the procedure is usually long and accompanied by complications during or soon after operation, or is performed on an organ more vital than most, such as the heart.<sup>12</sup> Sometimes the "simpler" procedures or diseases are also severely stressful enough to be causative associates; there are many reported examples<sup>8,13</sup> in association with appendicitis and appendectomy, strangulated hernia and herniorrhaphy.

The classic association with central nervous system tumor or trauma is well known. The reader's empathy and sympathy pours out to Cushing as he describes his helpless feeling of frustration and despair in relating the tragic ending of an otherwise successful removal of a brain tumor in death by exsanguination or perforation of a stress ulcer.<sup>4</sup> Birth trauma<sup>8</sup> and bulbar poliomyelitis<sup>14</sup> are other examples of central nervous system lesions which may be associated with acute ulceration. Bulger<sup>15</sup> reported upon a youngster (18 months old) who died following a snake bite. The snake was not identified, but as the venom is frequently specifically neurotoxic, it is of interest to note that coma and violent convulsions preceded the appearance of ulceration.

Even mental disease may precipitate a stress ulcer.<sup>16</sup> There are other examples, such as myocardial infarction,<sup>17</sup> too numerous to list. Some of them are shown in Table 2.

Many of the numerous and varied reported cases do have some things in common. The most striking is sepsis or shock. This association has been

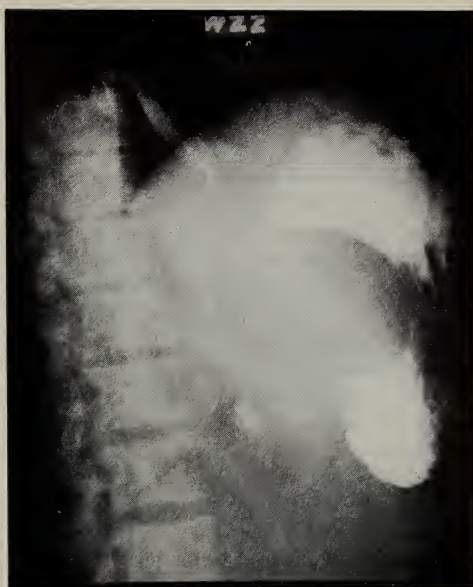


Figure 3.—X-ray film showing huge pancreatic pseudocyst in a 29-year-old man in whom stress ulcer subsequently developed. (Case described in text.)

noted and dwelt upon by several investigators.<sup>7,8,13</sup> Billroth<sup>13</sup> considered septic emboli to the gastric mucosa to be primarily responsible for death due to stress ulcer in a case in which he partially removed a huge substernal goitre.

The observation that many examples of stress ulcers, when studied microscopically, show widespread vascular thrombosis or congestion or both, has led to the view that hypoxia or hypotension may be specifically responsible for their development.<sup>18,19</sup> Experimental studies lend considerable support to this impression.<sup>20</sup> Harjola and Sivula<sup>21</sup> recorded some fascinating observations in rabbits. An initial episode of bleeding revealed a pale, white, relatively bloodless gastric mucosa. With restoration of blood volume several dark (hemorrhagic) spots would appear for a moment, then be gone. Repeated bleeding to the point of shock, however, led to frank dissolution and ulceration of parts of the gastric mucosa in many animals. The ulcers appeared in the very areas that became congested during the first bleed.

A different tack in experimental work was taken by French and Porter,<sup>22</sup> who found that acute gastrointestinal ulceration followed electrical stimulation of the hypothalamus in cats and that the effect



could be blocked in some instances by interruption of the vagus pathways.

Harkins<sup>1,2</sup> tabulated no fewer than 28 theories proposed as to how and why stress ulcers develop. The basic or most plausible of them have been covered or alluded to in the foregoing discussion, but the curious reader is referred to Harkins' articles for a complete review.

One theory we will never be able to pursue is that expressed by the ubiquitous John Hunter whose ideas from two centuries ago are frequently so modern that they tend to agree with our own current concepts. His views on the subject went up in smoke when the manuscripts containing them were accidentally burned.<sup>4</sup>

One cannot leave this aspect of the problem without mention of Dr. Wangenstein's angry dog. Apparently an enraged bulldog died from the effects of multiple stress ulcers which appeared after a spirited fight with one of his laboratory mates.<sup>23</sup> It is of interest to note that at autopsy the gastric acid was low.

## Clinical Behavior

The one clinical characteristic that all stress ulcers seem to have in common is that they appear without obvious warning and with dramatic suddenness. Prodromal symptoms and signs are absent. The only suggestion of an impending storm or disaster may be abdominal distension or ileus, though this is by no means always present. Hemorrhage of massive proportions or the effects of perforation simply present as both a fact and a challenge. The timing varies from a few hours after injury or operation to several weeks later. The great majority occur around the fifth to seventh day, or certainly within the first two weeks.<sup>24</sup> It is of great interest to note that if an acute stress ulcer is survived, with or without operation, there is little or no tendency to recurrence.<sup>25</sup>

## Diagnosis and Treatment

Observation in the necropsy room or operating theater is the only certain method of establishing the diagnosis. So many of the patients are so ill and kept to their beds by the primary disease process or by the encumbrance of a multitude of traction devices, cardiographs and intravenous tubing, that gastroscopy or radiography is seldom used. Both may be helpful, as they are in any diagnostic problem involving upper gastrointestinal hemor-

rhage. The diagnosis can certainly be very strongly suspected by association with a particularly stressful setting.

The difficulty of the therapeutic challenge is obvious to most of us from personal experience. The outlook has been indeed grim. Table 2 indicates how overwhelming the seriousness of the associated or precipitating disease processes may be. The table also indicates, however, that more often than not it was the ulcer that brought death. A characteristic of such cases is that often in retrospect there is the haunting thought that perhaps some of these unfortunate patients might have been saved with a well conceived and timely operation.

While it is true that some patients are basically untreatable, others are simply untreated (save for blood transfusion). The results tend to be poor.<sup>7,25</sup> Yet some patients do stop bleeding and recover with transfusion and other more obscure forms of non-surgical methods. Where does one draw the line? We "waited out" one of our patients to the total of 22 units of blood administered during the first postoperative week. This patient weighed over 400 pounds and had had jejunoileal bypass for exogenous obesity. Perhaps the surgeon's spirit was broken by the prospect of reoperation for control of hemorrhage in this case. In any event, bleeding stopped and the patient survived.

In another of our cases, dye was injected into the pancreas by misdirection in an attempt at aortography (at another hospital). Necrotizing pancreatitis was followed by shock, septicemia and pancreatic pseudocyst formation (Figure 3). The temperature reached 42.2°C (108°F). Somehow the patient survived all this; then bleeding began from a stress ulcer. The ulcer was suture ligated, the reasoning being that the patient's condition was such that he could not stand anything else. Bleeding recurred, and at reoperation the single gastric ulcer was found to have enlarged and to be bleeding furiously. It was excised and vagotomy and pyloroplasty were performed. The patient survived. These two cases emphasize that the most critical judgment must be exercised in deciding for or against operation in any individual case—operation according to the general rules, is the way Dalggaard<sup>26</sup> expresses it; or, in the words of Fogelman and Garvey,<sup>25</sup> "critically ill patients can withstand surgery better than they can withstand continuing hemorrhage, recurrent shock, and progressive deterioration."



Therapy: Choices, Results, and Rationale

It is not possible to make valid comparison of results as between non-surgical and surgical therapy. One reason is that in many patients non-operative treatment is not "elective" but is decided upon simply because of the incurable or hopeless nature of the primary disease. In other cases the bleeding ceases, does not recur, and the question of operation is never brought up. For that matter, the diagnosis is never really confirmed.

In the case of massive bleeders—patients who require five or more units of blood to maintain a reasonable volume during the crisis—the results of non-operative therapy are very bad. The reported mortality rates vary from 60 to 100 percent.<sup>7,25,27</sup>

Until the 1940s few patients had been operated upon for stress ulceration.<sup>1,2</sup> As recently as 1951, no survivals had been reported.<sup>25</sup> Since that time, reports of an increasing number of successes with operation have appeared in the surgical literature.<sup>7,23,24,25,27,28,29,30</sup>

Operations of various types have been used. At first it was local treatment with excision, closure or suture of the ulcer or ulcers, but often control of hemorrhage was not achieved and the ulcerative process progressed. More radical measures were tried. For a time a gastric resection, often quite high, was used. Although at times the procedure was successful, many deaths occurred. The logical next step in the search for improvement was vagotomy and pyloroplasty combined with local treatment of the ulcer. This is an "in between" procedure somewhat more simple to perform than resection and considerably more effective than local treatment alone. Current experience definitely seems to favor it (Table 3).

At first it was feared, not unreasonably, that any operation would end in disaster. After all, how could one operate through a burn wound and expect the suture lines to heal? Sometimes they did not. Hummel<sup>10,11</sup> reported two deaths after resection in such circumstances. One recalls Billroth's fear of elective operation on the stomach, wondering whether the gastric acid would dissolve away the closure of a gastrotomy incision.<sup>31</sup> The suture line healed in his first patient, and so they have in many cases since even when the patients were burned or otherwise badly injured.

At first glance the logic of a resection, with excision of the stressed mucosa and the mechanism that produced the ulceration, is difficult to argue against.

Two major objections can be raised, however. One is that stress ulcers do not often recur. The other is the prospect of problems and sequelae that are entailed in loss of much or most of the stomach forever. If the more conservative operation of vagotomy and pyloroplasty (plus local treatment) is really effective, and it seems to be, it obviously is the better procedure to use.

There is some scientific basis for the belief that vagotomy plays a key role in the control of stress bleeding. Womack and Peters<sup>32</sup> documented the fact that vagus section will result in the opening of submucosal and mucosal arteriovenous shunts in the gastric wall, with the result that blood is diverted from the surface mucosa to a significant degree, bleeding is thereby arrested and healing can go forward.

The effect of vagotomy on acid secretion during stress ulceration is less clear. There is no agreement that hyperacidity, relative or absolute, occurs

TABLE 3.—Results of Surgical Operation for Peptic Ulcer

Reported by	Resection		Re-Bleeding		Local Treatment		Re-Bleeding		V & P		Re-Bleeding		By-Pass	
	Survivors	Deaths	Survivors	Deaths	Survivors	Deaths	Survivors	Deaths	Survivors	Deaths	Survivors	Deaths	Survivors	Deaths
Hummel	0	2	..	..	..	..	..	..	..	..	..	..	..	..
Goodman and Frey	0	2	0	1	0	2	0	2	6	3	2	3	..	..
Wright	0	1	0	1	0	1	..	..	..	..	..	..	..	..
Fogelman and Garvey	4	1	..	..	..	..	..	..	1	2	..	..	0	1
Moncrief	1	5	0	1	..	..	..	..	0	1	0	1	..	..
Griffin	1	..	..	..	..	..	..	..	..	..	..	..	..	..
Biel	6	9	..	..	1	3	..	..	..	..	..	..	..	..
Gilchrist	3	0	..	..	..	..	..	..	..	..	..	..	..	..
Braithwaite	1	0	..	..	..	..	..	..	..	..	..	..	..	..
Wangensteen	2	3	..	..	..	..	..	..	..	..	..	..	..	..
Salasin	1	0	..	..	..	..	..	..	..	..	..	..	..	..
Bryant and Griffin	..	..	..	..	..	..	..	..	5	0	2	3	..	..
Kirtley, et al.	3	4	0	1	4	4	1	1	18	8	1	3	..	..
Nagel	0	4	..	..	1	1	..	..	6	2	0	1	..	..

at all. Dragstedt<sup>33</sup> thinks not. Yet the old adage "no acid, no ulcer" probably holds as well for stress ulcer as it does for the more typical variety.

Bryant and Griffin,<sup>34</sup> almost alone among recent observers, expressed belief that vagotomy and pyloroplasty is not the procedure of choice. All five of their patients had recurrence of bleeding and three died as a result. Their experience serves to emphasize there is no panacea and no perfect operation for this problem. Rebleeding does occur (as it does with gastrectomy also) and this complication ends in death far more often than not. Cumulative experience (Table 3) indicates, however, that the prospects for a successful outcome are significantly higher with vagus section and drainage than with either local treatment or subtotal gastrectomy.

In conclusion, it should be stated that the mortality rates in operation for stress ulcer tend to increase in direct proportion to delay in operation, no matter what procedure is used. The need for a carefully considered, but nonetheless quick decision is as great in dealing with this problem as it is in the management of a patient who is bleeding from a more typical peptic ulcer.

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## EXAMINING FOR UNDESCENDED TESTES

"The best position for examining a boy for undescended testes is to have him sit in a chair or on the examining table with his back against the wall and his heels brought up against his buttocks. The other technique . . . which is particularly helpful in the younger child, before cooperation is possible, is to apply some soap to the fingers and to rub the soapy fingers over the inguinal area. You will pick up the sensation of a testis rolling underneath your fingers when sometimes you cannot feel it."

ROBERT M. BLIZZARD, M.D., Baltimore

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# Interdepartmental Conference

FROM THE UNIVERSITY OF CALIFORNIA, LOS ANGELES, SCHOOL OF MEDICINE

## Influenza 1968—A2/Hong Kong/68

MODERATOR: JOSEPH W. ST. GEME, JR., M.D.

DISCUSSANTS: J. GLENN BRADLEY, M.D., DANIEL J. TORRANCE, M.D.,

FRANK M. HIROSE, M.D., DAVID T. IMAGAWA, PH. D.,

IRWIN ZIMENT, M.D., MARCEL A. BALUDA, PH.D., AND ICHIRO KAMEI, M.D.

DR. ST. GEME:\* We wish to present the tragic confrontation between a pregnant young woman and A2/HONG KONG/68 and in so doing correlate the clinical, radiographic, pathologic and virologic aspects of this epidemic viral infection. Later, we will plumb the tale more deeply and unfold our knowledge about the influenza virion and the various facets of resistance which are important to the host in this confrontation.

As a brief prologue while setting the stage for the presentation of the case, I would like to review the "Recommendations for Influenza Immunization and Control in the Civilian Population—1965-66" which was published in July of 1965 in the Morbidity and Mortality Weekly Report (MMWR) of the National Communicable Disease Center. The high risk groups for influenza immunization included persons with chronic debilitating diseases of cardiovascular, bronchopulmonary, and metabolic nature, the elderly, and pregnant women. "It is to be noted that some mortality was observed among pregnant women

during the 1957-1958 influenza A2 epidemic both in this country and abroad. It has not, however, been demonstrated in subsequent years."

The following recommendation was published in the MMWR of July 16, 1966: "Some increased mortality was observed among pregnant women during the 1957-58 influenza A2 epidemic . . . Similar data are not available for subsequent years and, therefore, routine influenza immunization during pregnancy is not recommended unless the individual also falls into one of the above noted high-risk categories."

In July of 1967 the Recommendation of the Public Health Service Advisory Committee on Immunization Practices was essentially the same. The MMWR of June 29, 1968, contained the recommendation that "routine vaccination of healthy groups of adults and children is not recommended. This recommendation is particularly relevant in 1968-69 because epidemic influenza is not expected to occur." Now these are the recommendations of mere mortals.

In the MMWR of August 31, 1968 there was a statement that in the preceding July influenza virus, A2/HONG KONG/1968, was isolated on the China mainland in the area of Hong Kong. The strains of virus isolated from this large outbreak

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showed a decided antigenic shift from previous strains. Similar viruses were subsequently isolated from an outbreak in Singapore. Significant concern developed that the United States was going to be confronted, some ten to eleven years following the 1957 epidemic of influenza (A2/JAPAN/305), with another large-scale epidemic.

The MMWR of August 31, 1968 contained the recommendation that the "currently available bivalent and polyvalent vaccine be given only to persons at highest risk of mortality or severe complications as a result of influenza." With the eventual availability of specific monovalent vaccine it was suggested that the chronically ill and the older age groups should be vaccinated or revaccinated with it. There was no comment about the pregnant woman.

We have asked Dr. Glenn Bradley of the Department of Obstetrics and Gynecology to present the clinical protocol concerning the previously mentioned unfortunate young woman.

### Fatal Influenza in Pregnancy

DR. BRADLEY:\* The patient was a 27-year-old, married, Caucasian woman, Gravida 4, Para 1, AB2, whose last menstrual period was July 20, 1968, and whose estimated date of confinement was April 27, 1969. She was admitted to Harbor General Hospital on December 27, 1968. She had received irregular prenatal care but her prenatal course was uncomplicated until five days before admission, when she noted the onset of chills, fever, productive cough, and shortness of breath as well as myalgia and headaches. Two days before admission she experienced increasing cough with mucoid sputum. On December 26, because of increased shortness of breath, she was put into hospital elsewhere with a diagnosis of pneumonia and treated with tetracycline. An x-ray film of the chest was suggestive of possible tuberculosis and she was referred to Harbor General Hospital.

She had rheumatic fever at age 10, requiring bed restriction for several months. She was allergic to penicillin and lincocin. There was no familial history of tuberculosis. Her father had died of carcinoma of the lung.

When examined, the patient was observed to be thin. She was sitting up in bed in moderate respira-

tory distress with obvious tachypnea. Blood pressure was 116/70 mm of mercury, pulse 120, respirations 50 per minute and shallow, and temperature 38.3°C (101°F). Respirations were symmetrical and the diaphragms moved easily. Generalized bronchial breath sounds were detected, with diffuse rhonchi and moist rales. The heart had a regular rhythm and the third heart sound was audible. There was a questionable opening snap, but no murmurs were heard. The abdomen was soft and the fundus was palpable two fingerbreadths above the umbilicus. There were irregular moderate-quality uterine contractions every five to seven minutes. The estimated fetal weight was only one pound. Fetal heart tones were regular, 120 per minute. The cervix was 90 percent effaced, the os closed, and the vertex was at —2 station. There was suggestive slight cyanosis of the nailbeds, and the skin and mucus membranes were mildly cyanotic. The impression on admission was influenzal pneumonia complicated by secondary bacterial infection.

Admission laboratory data included a leukocyte count of 13,700 and hematocrit of 28 percent. Two days later leukocytes numbered 15,800 with 56 percent bands, 39 percent polymorphonuclear cells and 5 percent lymphocytes. Plasma electrolytes were unremarkable and blood gas analysis revealed a pH of 7.39, pO<sub>2</sub> of 66, pCO<sub>2</sub> of 32, and an oxygen saturation of 93 percent. A Gram stain of the sputum revealed many white cells and a moderate number of Gram-positive diplococci. Urinalysis was within normal limits. An x-ray film demonstrated massive infiltration and consolidation of both lung fields with obscuration of the cardiac shadow. (This and subsequent films will be discussed later.)

The patient was given cephalothin, nasal oxygen, and intermittent positive pressure assisted ventilation. The patient's temperature remained at 38.3°C, occasionally spiking to 39.4 (103°F). The blood gases remained unchanged. Because of the low hematocrit, 2 units of packed erythrocytes were administered. A consultant suggested that the patient would benefit from a pulmonary lavage, which was performed under general anesthesia. At the time of the lavage the patient had cardiac arrest for approximately 5 minutes but responded to conservative measures of resuscitation. A tracheostomy and bronchoscopy were performed, and specimens submitted at that time yielded viridans streptococci, the same organism

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that was cultivated from the sputum on admission (virologic studies will be discussed below. See also Table 3).

The patient was placed on a volume respirator. Following the pulmonary lavage there was some improvement in pulmonary findings. Cephalothin was continued and digoxin and cortisone were added. Blood gases were determined serially. The profound acidosis (pH 7.01) following cardiac arrest was corrected progressively by the administration of bicarbonate and calcium gluconate. Chest films following pulmonary lavage revealed little change. Fifteen hours later minimal clearing of the infiltrate was noted. The patient was placed on the volume respirator again and an anectine drip was required to keep her from resisting the apparatus. On the fourth hospital day sinus tachycardia and supraventricular tachycardia occurred. Soon thereafter severe subcutaneous emphysema involving the upper torso, the neck and face was observed. An intratracheal tube was inserted at the tracheostomy site. A second cardiac arrest occurred, and resuscitation restored spontaneous cardiac activity. Films of the chest at that time showed severe pneumomediastinum, but no pneumothorax. During an attempt to place a cuffed endotracheal tube, cardiac arrest occurred again but this time resuscitation was unsuccessful. The patient was pronounced dead five days after admission to the hospital.

DR. ST. GEME: So that we may develop an expanded view of our recent experience with epidemic influenza, our colleagues will discuss the radiographic, pathologic, and virologic aspects of several cases in addition to that of the young woman described above.

## Radiographic Features

DR. TORRANCE\*: It would be difficult, looking at the admission chest film (Figure 1) in the case of this young woman, to diagnose viral pneumonia or influenza pneumonia. One would place other entities higher in the differential diagnosis. The picture is that of an overwhelming exudative process in the pulmonary alveolar spaces. One could not comment on the presence or absence of interstitial involvement. There is no direct evidence of it. Our initial diagnostic consideration would be

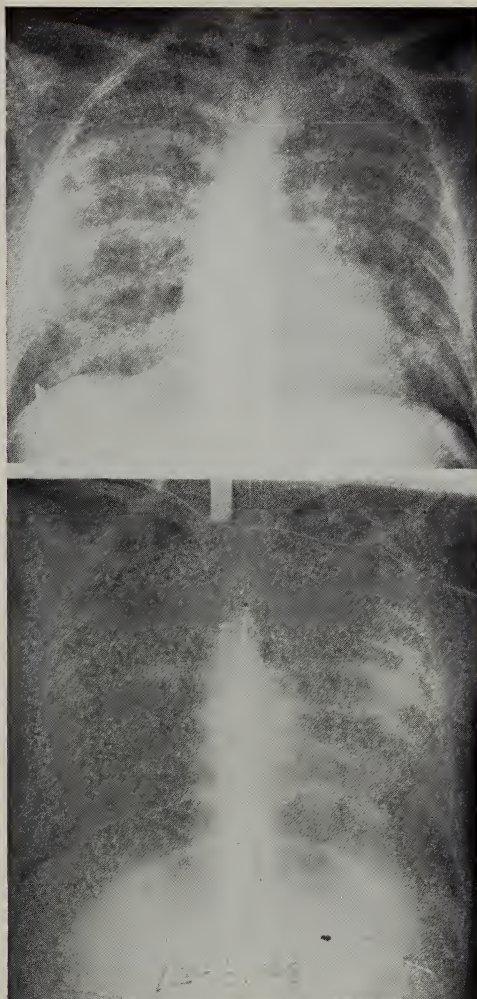


Figure 1.—X-ray films of chest in propositus case. *Above*, diffuse influenza virus pneumonitis on the day of admission. *Below*, extensive change throughout both lung fields shortly before death.

one of overwhelming pulmonary edema. We have seen films resembling this one in heroin addicts, following the injection of the drug with whatever is used to "cut" it. We have seen the same radiographic pattern in overwhelming intoxications, with extensive aspiration, with sudden acute overwhelming left ventricular failure, and with acute hypersensitivity reactions as in transfusion reaction. All these diagnoses must be allotted their place and rank in the evaluation of each film.

\*Daniel J. Torrance, M.D., Professor of Radiology, UCLA School of Medicine; and Chief of Radiology, Harbor General Hospital.





Figure 2.—The patient in this case was a 33-year-old pregnant woman with diffuse influenza virus pneumonitis. This film was obtained after pulmonary lavage, shortly before death.

We see next rapid extension of the infiltrate to involve all segments of both lungs diffusely and symmetrically (Figure 1). In this film we can assay how extensive it has become from the well-defined air bronchogram, indicating massive consolidation. This film was taken after the pulmonary lavage and shortly before death.

This next chest film (Figure 2) looks as though it might represent the same patient. However, it was of another young woman, also pregnant, who was admitted with a similar history and subsequent rapid deterioration and death.

It is important to emphasize that the films of these two different patients were taken after pulmonary lavage, and one wonders what role this attempted flushing of the lungs played in the development of these radiographic patterns.

The last film (Figure 3) obtained from an elderly woman with virologically documented influenza, shows still another pattern—that of focal lobular pneumonia, which may be associated with some tissue breakdown. There is coarse “honeycombing” or excavation, a finding that might suggest staphylococcal pneumonia rather than influenza. This patient died shortly after admission to

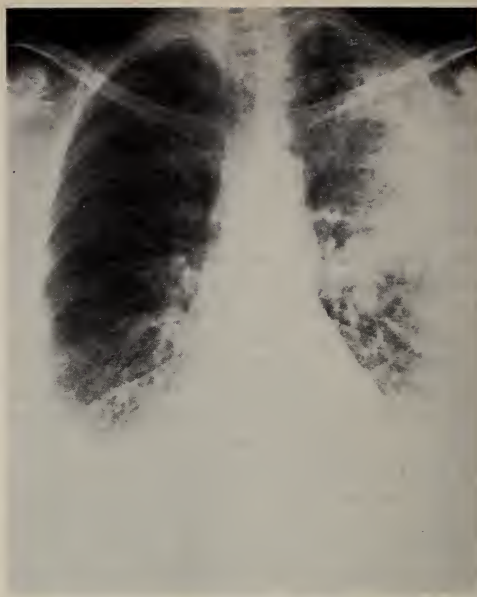


Figure 3.—X-ray film of chest of 66-year-old woman with chills, fever, and cough three days before admission to hospital with staphylococcal bacteremia (Case 1, Table 2). Death ensued within 12 hours of admission and influenza virus was isolated from lung tissue at necropsy.

hospital with staphylococcal bacteremia, and influenza virus was isolated from the lung at necropsy.

When we review the literature for descriptive treatment of the radiographic changes in these viral pneumonias, we can approximate accurate summary by saying that “anything is possible.” The lesion can mimic any other infection, focal or diffuse, or even pulmonary edema.

### Pathology

DR. HIROSE:\* In December of 1968 we encountered for the first time in our autopsy suite a relatively unusual situation, a very severe tracheo-bronchitis with pronounced hyperemia of the trachea and associated areas of purulent exudate. This was puzzling but we were aware that influenza virus was present in our patient population. The most striking finding at necropsy was the voluminous lungs observed in six patients that we believed had influenza. In four of the six cases the influenza virus was isolated. In the other two the morphological features were so characteristic that we felt confident that the diagnosis was influenza.

\*Frank M. Hirose, M.D., Assistant Professor of Pathology, UCLA School of Medicine; and Staff Pathologist, Harbor General Hospital.



The gross autopsy diagnosis of influenza is suggested by tracheobronchitis, with pronounced hyperemia of the upper respiratory tract, and enormous distended extremely heavy lungs.<sup>1</sup> The lightest lungs of our series weighed 1,650 grams, which is at least twice the combined weight of normal lungs, and the range was up to 4,000 grams.

Consistent with the remarkable tracheobronchitis seen grossly, microscopically there is desquamation of the respiratory epithelium with exposure of a necrotic and edematous lamina propria (Figure 4). In spite of extensive necrosis of the lamina propria region, there is scant inflammatory reaction in the subjacent tissues. Focally, ducts leading to the mucous and mucoserous glands are lined by squamoid regenerative epithelial cells. The grossly seen hyperemia is due to pronounced dilation and congestion of the subepithelial vessels and diffuse hemorrhage throughout the stroma.

The purulent and necrotizing process extends down into the bronchi and the bronchioles, where there is also desquamated and regenerative epithelium. In the alveolar region proliferation of alveolar epithelial cells is evident. One may also see the classical histological feature of the pulmonary parenchyma in influenza, hyaline membranes (Figure 4). Hyaline membranes are characteristic of influenzal pneumonitis, yet based on this observation alone one cannot state that the morbid process is influenza. Hyaline membranes may also be seen in radiation, uremic and rheumatic pneumonitis, or in oxygen toxicity in its early stages.

With the passage of time thrombi are found in capillaries of the alveolar wall, and extravasation of blood can be seen within the alveolar lumina.

In addition to hyaline membranes, there are thickened alveolar septae. One could suggest that interstitial pneumonitis and diffuse edema cause the excessive weight of the lungs.

Superimposed infection may lead to areas of bronchopneumonia. So the lungs of influenza at necropsy are at times clouded by the presence of other types of infectious processes, and in the past pneumococci, streptococci and staphylococci have been implicated in the pathogenesis of fatal influenza.

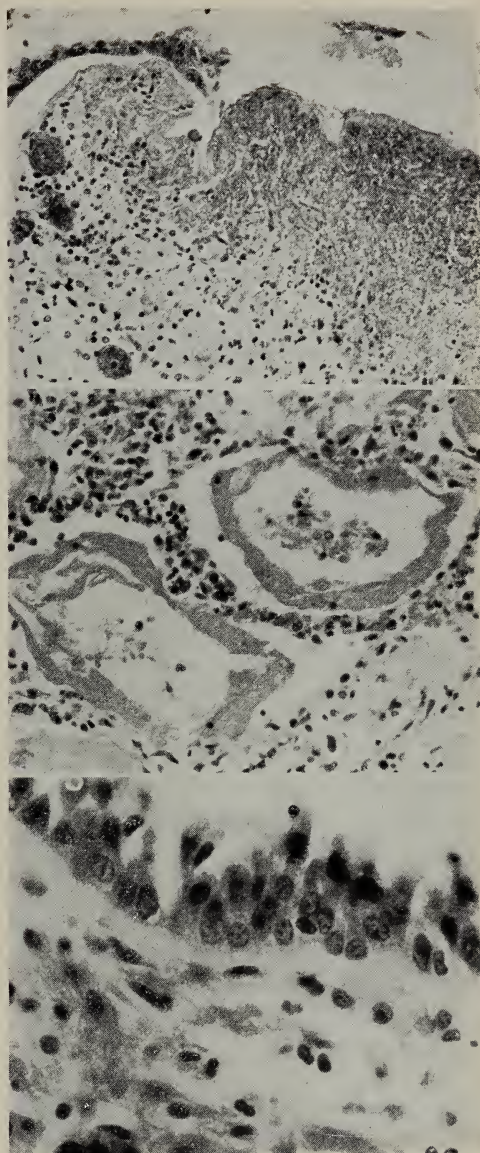


Figure 4.—Photomicrographs in propositus case. *Above*, acute tracheitis with loss of epithelium, necrosis and edema of the lamina propria. (Hematoxylin and eosin stain. Medium power.) *Center*, hyaline membranes lining alveoli of lungs. (H. & E., medium power.) *Below*, the mucous membrane of a bronchus with prominence of the basement membrane. (H. & E., high power.)

One of the most characteristic features of influenza is the desquamation and necrosis of epithelium, and, in addition, an adjacent concomitant regeneration of the epithelium. This seems to be a unique feature. At high power microscopic visualization, variability of the nuclei of the bronchus and bronchiolar epithelial cells is well shown. If there happened to be available a Papanicolaou-stained sputum containing epithelium of this type it would alarm the cytologists. The atypical cells would be suspect for malignancy. One wonders if the variability of the nuclei of the epithelial cells is a result of stimulation of epithelium by the virus.

Pronounced thickening of the basement membrane is also a feature of the lung in influenza (Figure 4).<sup>2</sup>

Some of the accompanying disease processes which were present in the six necropsy cases at Harbor General Hospital are described below. Our patient for primary discussion was pregnant. The fetal lung did not show hyaline membranes, nor was the virus recovered by culture.

In another patient, the coronary arteries were severely affected by arteriosclerosis, and the heart was compromised by very decided myocardial fibrosis.

In a third patient, a lymphoproliferative state consistent with lymphosarcoma was noted in the peripheral and visceral lymph nodes. One wonders about the altered immunological state in patients with such a disorder and their ability to resist the onslaught of influenza virus.

The fourth patient, a relatively young person, 44 years, had a subclavian steal syndrome. There was pronounced occlusion of the major vessels of the arch of the aorta, unilateral renal atrophy, and thrombosis of the aorta. The fifth patient had cirrhosis of the liver.

The morbid anatomy of influenza seen at autopsy in 1968-69 has been reviewed. Is there something new being recorded? In a relatively ancient monograph, published in 1920 by Dr. Winternitz,<sup>3</sup> there is shown the classic feature of influenza, namely, tracheobronchitis with pseudomembraneous exudate and profound hyperemia of the tracheobronchial tree.

The lungs are pictured as being voluminous and distended, with firm, edematous, hyperemic parenchyma and occasional bronchopneumonia. Scattered foci of alveolar hemorrhages can be found. On cut sections, gray infiltrates are reminiscent of

an interstitial fibrosis or fibrin deposition. The extremely heavy lung, the voluminous lung, the edematous wet lung, and the lobar involvement are emphasized. Influenza is called a "panlobar" pneumonia.

Depicted histologically is the tracheobronchitis manifested by necrotic epithelium, a hyperemic lamina propria, and the relative paucity of the acute inflammatory exudate in the lamina propria. Classic hyaline membranes and extravasation of blood into the alveoli may be seen. The gross diffuse grayness of the parenchyma is identified microscopically as diffuse fibrin deposition.

So, the morphology of influenza 1968-69 has been duplicated or revisited and in essence is similar to that which was described in 1920 by Dr. Winternitz.

### Laboratory Procedures

DR. IMAGAWA\*: As in most other viral infections, the laboratory procedures for influenza diagnosis would include isolation of the etiological virus or the demonstration of specific antibody rise in the patient's serum. During the recent epidemic we relied primarily on the isolation of the influenza virus with subsequent typing and identification of the isolates. Virus isolation would be an important procedure for identifying the agent responsible for an epidemic. Once the prevailing virus is isolated and typed, diagnosis of other cases can be carried out by serological methods.

The laboratory host of choice for the isolation of influenza virus is still the chick embryo. Fertile eggs incubated for 10 to 14 days are inoculated into the amniotic sac. After two to four days of incubation a specimen of the amniotic fluid is tested for hemagglutinating activity.

Isolation of influenza virus has been accomplished also by inoculation of primary monkey kidney cell cultures. Generally on primary isolation, the virus does not cause clear-cut cytopathic effects, and the presence of the virus must be detected by an indirect method. Since influenza virus possesses hemagglutinins, a technique described as hemadsorption can be used. This is a procedure in which the hemagglutinins on the infected cell surface cause the red blood cells to adhere in clumps to the host cell monolayer.

We employed both the chick embryo and the

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TABLE 1.—A2/HONG KONG/68 Isolates from Seven Ambulatory Patients

Age	Diagnosis	Specimen	Onset of Illness	Specimen Taken
Adult	Influenza	Throat swab	12/ 3/68	12/ 3/68
Adult	Pneumonia	Sputum	12/ 4/68	12/ 9/68
Child	Vomiting and diarrhea	Throat swab	12/ 7/68	12/ 8/68
Child	Influenza	Throat swab	12/15/68	12/17/68
Child	Influenza	Throat swab	12/14/68	12/15/68
Child	Influenza	Throat swab	12/14/68	12/14/68
Child	Influenza	Throat swab	12/16/68	12/17/68

TABLE 2.—A2/HONG KONG/68 Isolates from Postmortem Materials

Patient	Sex	Age	Specimen	Virus Isolation
1	F	66	Bronchus	Cell culture + Egg +
2	F	60	Lung	Cell culture + Egg +
3	M	44	Lung	Cell culture + Egg +
4	F	27	Lung	Cell culture — Egg +

cell culture procedures for isolation of influenza virus. The freshly isolated viruses were identified as strains of A2/HONG KONG/68 by the hemagglutination-inhibition and the hemadsorption-inhibition tests.

The isolation of A2/HONG KONG/68 virus strains from seven ambulatory patients is summarized in Table 1. These isolates were made in monkey kidney cell cultures. Successful isolation of the viruses can be credited to the very short interval between the onset of the disease and the obtaining of clinical materials for inoculation. Specimens for viral isolation attempts were obtained as early as possible in the course of illness.

Table 2 summarizes the isolation of the epidemic strain of influenza virus from postmortem materials. Both the monkey kidney cell culture and the chick embryo procedures were used. Virus isolation was accomplished from the bronchus or from the lungs. Both isolation techniques yielded the virus, with the exception of the lung from the case under discussion (Case 4, Table 2) which yielded no virus with the cell culture method but was positive by the chick embryo procedure.

Table 3 summarizes the virus isolations in the case presented in this conference. On December 12, 1968, before the patient died, the lung lavage and the sputum inoculated into monkey cell culture yielded influenza virus A2/HONG KONG/68. The postmortem material from the lung inoculated into cell culture was negative, but the chick embryo system yielded virus. The tracheal epithelial ma-

TABLE 3.—A2/HONG KONG/68 Virus Isolation from Case Discussed in Present Interdepartmental Conference

Date	Specimen	Virus Isolation
12/30/68	Lung Lavage	Cell culture +
	Sputum	Cell culture +
1/ 2/69	Lung	Cell culture — Egg +
	Tracheal Epithelium	Cell culture — Egg +
	Heart	Cell culture —
	Placenta	Cell culture —
1/ 2/69	Fetal lung	Cell culture — Egg —
	Fetal heart	Cell culture — Egg —

terial inoculated into cell culture was again negative, whereas the chick embryo was positive. It would appear from these studies that there is a higher rate of isolation in eggs than in cell cultures. However, it is the opinion of most investigators that the rate of isolation is essentially similar in eggs and in cell cultures. Virus was not recovered from the placenta and the heart; likewise, the heart and the lung from the fetus yielded no virus.

Finally, I would like to discuss briefly the relationship between Hong Kong 1968 strains and the earlier A2 strains. It was recently reported that antisera produced against Hong Kong 1968 strains clearly demonstrated an antigenic relationship with the earlier A2 viruses.<sup>4</sup> However, the Hong Kong influenza viruses represented a major antigenic drift and the identification of the Hong Kong strains may not be possible with specific antisera produced against the earlier A2 reference strains. Nevertheless, these new isolates are still classified as A2 influenza viruses.

DR. ST. GEME: The provocative clinical and laboratory facets of the 1968 epidemic, as we witnessed it in our own medical center, raise the most fundamental questions of the innate resistance of the human host and the complexity of the genetic, antigenic and biochemical attributes of the influenza virus. The following sections of this conference represent an attempt to acquire some perspective of these questions.

### Host-Virus Relationship And Lower Respiratory Tract

DR. ZIMENT\*: First of all I think we should clarify that the virus we are talking about did not really originate in Hong Kong in July 1968; the evidence

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is that it originated in China and that it was probably a fairly close relative of its notorious predecessor of 1957. It used Hong Kong as an embarkation point for a world cruise and it landed in Los Angeles roughly five months later. Its subsequent depredations resulted in this symposium.

Infection of a host by the influenza virus can occur when the agent encounters the susceptible respiratory mucosa. The cilia of the epithelium present receptor areas to which the influenza virus becomes very firmly attached, causing inhibition of ciliary activity. The goblet cells are also affected, and lose their ability to produce mucus, which in turn may increase the mucosal susceptibility to further invasion.

Following the invasion of the respiratory mucosa there may be a lag phase; thus, members of a family may derive their initial infections at different periods yet symptoms may develop in all of them simultaneously. This is probably related to the fact that external factors initiate the breakdown in the host-virus relations, and perhaps chilling or a change in weather are important determinants in the development of symptoms. Viral pathogenicity probably depends upon the release of toxic products, some of which are purely speculative. It is well known that the virus inhibits the chemotactic response of the leukocytes, and it also appears to inhibit the ability of the granulocytes to engulf bacteria.

The virus inhibits the cilia of the epithelium and, subsequent to that, causes death of the cells; it appears that the goblet cells are also killed. If the virus invades the lower reaches of the respiratory tract, it similarly destroys the various types of cells lining the bronchioles and alveoli. In particular, the pneumocytes known as Type I cells, and the macrophages known as Type II cells are damaged and lose contact with the basement membrane, thus contributing to the formation of a hyaline membrane. A true alveolar capillary block seems to be produced, and it is also possible that surfactant is damaged, leading to micro-atelectasis. As a result of all these changes the alveoli are severely damaged and pronounced hypoxia may result.

It is well known that pregnant women are particularly liable to the ill effects of influenza pneumonia.<sup>5,6</sup> This is well illustrated in the patient who is presented in this conference. She was five and a half months pregnant, and at that time in pregnancy the patient suffers several disadvantages of hemodynamic and pulmonary function. The dia-

phragm is elevated and there may be associated atelectasis in the basal parts of the lung; there is an increased hemodynamic load, and an increased oxygen requirement imposed by the fetus and placenta. The heart is less able to make a full compensatory adjustment to the stress of infection, and the addition of severe pneumonic involvement exacerbates the tendency toward hypoxia. The presence of heart disease will obviously embarrass the situation further, and many of the deaths in epidemics have been associated with the presence of mitral stenosis and pulmonary hypertension. It is not clear whether the pregnant woman is also at a disadvantage from other than these purely mechanical factors. Thus, it is possible that there is impaired production of the various antiviral factors or of surfactant.

The toxic effects of the virus infection may result from release into the bloodstream of antigenic material both from the virus and from the damaged tissues. The patient has a generalized illness and in some cases there may even be an allergic reaction to viral products, but the dangers of the disease are associated with the embarrassment to the respiratory process and the resulting hypoxia. Secondary bacterial infection of the lung is an important complication, and staphylococcus aureus, for unknown reasons, is particularly likely to complicate influenzal pneumonia.<sup>5</sup> The virus certainly prepares the way for bacterial infection by disruption of the respiratory mucosa and by damage to the underlying blood vessels, as well as by inhibiting phagocytosis.

This review of the host factor is based on accepted and well understood phenomena, but to move on to how the host reacts against the virus is to tread on ground which is not so steady at all. However, it appears that the immunologic response to influenzal respiratory infection will be incomplete, since the bloodstream is not invaded in the usual case. Defense against the virus depends in part upon the production by the host of immunoglobulins. The specific immunoglobulin that is most important to the respiratory tract is IgA, and this is secreted by the mucosa. It also is formed in the bloodstream, and the amount in the mucosa is perhaps only one-tenth the amount in the blood. But it is of considerable interest that persons with agammaglobulinemia are able to react quite normally to viral infections, so obviously immunoglobulins do not play a major role. It is evident that lymphocytic factors also are involved, for in pa-

tients with impaired delayed hypersensitivity severe generalized disease may occur in virus infections.

It has been clearly established in the last few years that viral infections of almost any type stimulate the host to produce a curious protein called interferon.<sup>7</sup> Time does not permit discussion of the very complex nature of the mechanism involved in the production and action of interferon, but its production is primarily a result of viral infection of the cells, although it is quite possible that many other factors which occur both normally and abnormally influence the mechanism.

The survival of the virus is facilitated by the production of several postulated rather than absolutely confirmed factors, and these rejoice under rather curious names, such as stimulon, enhancer, and blocker, which in one way or another interfere with the action of interferon.<sup>7</sup> Similarly, viral enzymes such as neuraminidase facilitate viral pathogenicity. On the other hand, the host is able to respond to the viral infection by producing a number of equally ill-understood non-specific inhibitors: in particular the literature refers to alpha, beta and gamma inhibitors, which are either mucoproteins or lipids or other complex proteins.<sup>8</sup>

The host probably does offer resistance in various other ways about which we can only speculate. Thus influenza is more likely to occur in persons who are of blood group O, although there is no further explanation as to why this should be.

Regarding the therapy of our ill-fated patient, I wish to state that we felt pulmonary lavage was justified since we were dealing with an alveolar filling defect, with some similarities to alveolar proteinosis which responds well to lavage.<sup>9</sup> The role of specific drugs is not yet established, and the only drug which has been commercially available for use in influenzal infections is amantadine hydrochloride, which interferes with the ability of the virus to penetrate the cell. This has been found to be of specific value in the prevention of A2 influenza infection, but its use was not recommended by the Public Health Service. We were left with as primitive a way of dealing with this epidemic as we had in 1957.

## Genetic Aspects of Antigenic Drifts of Influenza Virus

DR. BALUDA: \* Although not until the 1930s was it established that a virus was the causative factor

in influenza, the disease is not a new malady of the human population.<sup>10</sup> There are descriptions of influenza infections in humans and in animals which date from the 12th century, and 31 pandemics have been recorded since the 16th century. Three major pandemics have occurred within the past 50 years; the last one, referred to as the "Hong Kong Flu," appeared in 1968. During these pandemics, almost the entire population is exposed and develops antibodies against the virus. Every time there is a major epidemic, it is caused by a new virus. This periodic appearance—approximately every 10 years—of a new virus capable of infecting a previously immune population is a unique feature of influenza viruses and is due to a phenomenon called "antigenic drift." The new virus contains a different, or modified, antigen on its outer surface and is not neutralized by antibody made against the old viruses. This means that not only can the new virus infect a population exposed to the old viruses, but prophylactic vaccination with known strains is either ineffective or only moderately effective. Stable variants, or strains, differing in antigenic properties are known to exist among all viruses, but the regular appearance of new influenza viruses had been a puzzle to virologists and epidemiologists. Only recently has it been possible to understand this unique nature of influenza virus, albeit without knowing how to cope with it.

Before attempting an explanation for the basis of this antigenic drift, let us first examine the structure of the influenza virion and its mode of replication.

## Structure of Influenza Viruses

Influenza viruses contain about 0.8 percent RNA, 74 percent protein, 18.5 percent lipids and 5 to 7 percent non-nucleic acid carbohydrates.<sup>10</sup> In the electron microscope, influenza virions appear pleomorphic ranging from spherical to filamentous forms with a diameter of 800-1,100A (angstrom units).<sup>11</sup> The inner core of the virus, or ribonucleoprotein (RNP), consists of the RNA genome complexed with protein and is a rather flexible rod-shaped structure with subunits which appear to be in a helical arrangement.<sup>12</sup> The RNP core is enclosed in a lipoprotein envelope which has cylindrical spikes on its outer surface. These spikes, 90A long and 15-20A in diameter, appear to consist mostly of hemagglutinin, the protein which agglutinates erythrocytes. Between the spikes

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there is another protein, neuraminidase; this enzyme digests mucoproteins and facilitates the release of virus during its maturation from the cell surface. The viral envelope contains lipids which are mostly of cellular origin and some host cell antigen—for example, blood group antigen.

### *Antigenic Structure*

Three major antigens are used in classifying influenza viruses<sup>13</sup>:

1. One is the internal antigen, also called RNP antigen, which determines whether the virus is type A, B or C. This antigen is detected by complement fixation and is referred to as the CF (complement fixing) antigen. The ribonucleoprotein is a stable component of the virus as determined by its antigenicity—that is, it is the same for all members of the type A group regardless of whether they infect man, swine, horse, duck or chicken. Minor variations in primary amino acid sequence, not detectable by complement fixation, cannot, however, be ruled out. The RNP antigen is a peptide with a molecular weight of  $50\text{--}70 \times 10^3$  daltons.

2. The hemagglutinin antigen (HA) on the spikes, also referred to as the "V" antigen, is detected by virus neutralization, or hemagglutinin inhibition, and is strain-specific—that is, it is different for strains A0, A1, A2, and others. This is the antigen which elicits the formation of protecting antibody. A new virus, capable of causing an epidemic, must possess a hemagglutinin which is sufficiently different so that it is not neutralized by antibodies made against that of the existing strains. HA subunits obtained by disrupting the virus with detergent—e.g., deoxycholate—consist of glycoprotein rods, 140A long x 40A wide with a molecular weight of 47 to  $75 \times 10^3$  daltons. The individual rods are monovalent—that is, can block red cell agglutination but are incapable of causing red cell agglutination. In the absence of detergent, they clump and appear as rosettes in the electron microscope; the rosettes can cause agglutination of red blood cells. The host antigen, which is present in the envelope, is a carbohydrate and is covalently linked to the hemagglutinin subunits.

3. The other major virus antigen which is present in the envelope is the neuraminidase (NA). This enzyme differs serologically and chemically from HA and can vary independently of HA. Antibodies against this enzyme do not appear to play a major role in protection against virus infection,

although the antineuraminidase antibody may limit subsequent infection by preventing the release of virus from infected cells. Purified neuraminidase units are oblong structures about 85A long and 50A wide with a centrally attached fiber 100A long and a diffuse tail, or a small knob, of 40A in diameter. These particles consist of peptides with a molecular weight of  $50 \times 10^3$  daltons which are probably linked to the HA unit through the carbohydrate moiety in the virion.

Other proteins which make up less than 10 percent of total virion protein and appear as peptides of molecular weight less than  $20 \times 10^3$  daltons in gel electrophoresis have not been characterized.

### *Viral Genome*

The genome of influenza viruses consists of single stranded ribonucleic acid (RNA). It has some unique features which hold the clue to the antigenic drift. Unlike the genome of other single stranded RNA viruses, the influenza virus RNA is heterogeneous and consists of 4 to 5 molecules of varying sizes ranging from  $7 \times 10^5$  daltons to  $2 \times 10^6$  daltons in molecular weight.<sup>14,15</sup> Five distinct species of viral RNA have been separated by gel electrophoresis.<sup>16,17</sup> From the profile of the viral RNA in sucrose gradients and in gel electrophoresis, it appears that these RNA molecules are present in a 1:1 ratio in fully infectious (complete) virus. In incomplete (von Magnus effect) virus the larger species are either absent or present in only 2 percent of the virions.<sup>18,19</sup>

### *Virus Replication*

The replication of influenza virus can be divided into three major phases: (1) replication of the RNA genome, (2) synthesis of viral proteins, and (3) maturation and release of virions at the cell surface.

1. As with other RNA viruses, the replication of influenza RNA depends upon a virus specific enzyme, RNA-dependent RNA polymerase. Complementary RNA, or minus strand, is made using the incoming viral RNA as the template, and in turn it is used to make new plus (viral) RNA strands.<sup>20</sup> The synthesis of new viral RNA takes place via an RNA replicative intermediate (RI) which consists of one minus strand to which are attached several nascent plus strands.<sup>21</sup>

2. Viral RNA acts as messenger RNA for making virus-specific protein, for example HA, NA, internal



protein and RNA dependent polymerase. Recently polysomes involved in the synthesis of peptides were isolated from infected cells and were found to contain both plus and minus RNA strands.<sup>22</sup> The location of different genes in the different strands of viral RNA is unknown.

3. Maturation involves packaging different RNA species in the form of ribonucleoproteins into an envelope which is made at the cell membrane but contains mostly viral antigens. There should also be a mechanism for excluding minus strands which are not found in virions. Nothing is known about the processes involved. Maturation is completed as the virion buds off the cell surface.

#### *Mechanism of Antigenic Drift*

According to the current dogma of molecular biology, the antigenicity of the viral coat protein is determined by its amino acid sequence, which in turn is coded by the sequence of nucleotides in the viral genome. Any major antigenic shift is therefore the phenotypic expression of a different viral genome. The evolution of a genetic variant can take place either by mutation, genetic recombination or strand exchange.

**Mutation:** Due to spontaneous mutations or to errors in copying the nucleic acid, there may be occasional alterations in the base sequence of the RNA which in turn causes changes in the amino acid sequence and in the antigenicity of the protein. A mutation in the hemagglutinin gene could give rise to a new variant. Most of the stable variants of RNA viruses arise by mutation and selection.

Mutations have also been shown to cause variations among influenza viruses. In the laboratory, such mutant strains can be obtained in various ways; for example, mutants involving changes in the virus coat protein can be obtained by growing the virus in the presence of antiserum of low avidity.<sup>23</sup>

Minor outbreaks of influenza between the major pandemics are often caused by minor changes in virus coat protein which arise by mutation and selection. However, mutation alone cannot explain the high frequency of appearance of a new influenza virus strain every eight to ten years, since similar changes do not take place among other single stranded RNA viruses—such as mumps, rubella, measles, polio, NDV and arboviruses—which infect man and animals. It is well established that these viruses can also develop variants or mutant strains, but the mutant viruses are stable and, un-

like influenza viruses, can be isolated in recurring epidemics.

**Genetic Recombination:** The second possibility of forming a new virus is by recombination, which involves the exchange of covalently linked parts of the genome between two or more viruses growing in the same host. Thus the progeny virus will have new genetic material which is a hybrid of the two parent viruses. Recombination occurs regularly among DNA viruses. This process of exchange takes place by excision and ligation of double stranded DNA. The relatively stable secondary structure of DNA is almost an absolute requirement for such an exchange. It is not known whether such a mechanism of recombination between RNA viruses exists. Using DNA virus as a model, one would expect that recombination can only take place between two double stranded RNA molecules or between replicative intermediates which are partially double stranded. However, since there is preferential replication of plus (viral) RNA strand, there are relatively few RI's compared with the number of plus strands formed,<sup>21</sup> and the chances of recombination between the RI's of RNA viruses is much less than that between the DNA's of DNA viruses. Indeed, recombination is a rare event among RNA viruses. With Newcastle disease virus, heterozygotes and phenotypically mixed virions can easily be obtained by infecting a host with two different strains,<sup>24</sup> but recombination has not been demonstrated conclusively. With poliovirus, at the most 0.4 percent of the progeny viruses might be hybrids resulting from recombination.<sup>25</sup> On the other hand, hybrid viruses can easily be formed by infecting cells with two different influenza viruses.<sup>26,27</sup> The percentage of hybrid virions in the progeny can be as high as 94 percent of the total virions.<sup>26</sup> So high a frequency of hybrid formation cannot be explained by classical recombination.

**Strand Exchange:** Strand exchange will be defined as the process that involves exchange of genetic material between two or more viruses growing in the same host but, unlike recombination, it does not involve breakage and reformation of covalent linkages in the genomes involved. This process can take place only in viruses which contain a genome consisting of multiple subgenomic fragments, and thus far it is unique for influenza viruses. In the laboratory, numerous experiments have shown that hybrid virus formation does take place with unusually high frequency if cells are infected with two influenza virus strains.<sup>27,28</sup> The

more related the two infecting virus strains, the higher is the percentage of hybrid virus in the progeny; in chick embryo cells infected with ws and wsn strains, 10 to 94 percent of the progeny may consist of hybrid virions.<sup>26</sup>

Recently, using temperature-sensitive (ts) mutants, it has been found that all ts mutants can be classified into five groups.<sup>28</sup> Exchange of genetic information was possible between the groups, but not within any one group. Exchange of genetic information and formation of hybrid virus have also been shown to take place between animal and human viruses. A classical example of hybrid formation is the x-7 virus obtained by crossing AO NWS (a human strain) with A2-Singapore, 1957 (a strain infecting man, ducks and turkeys).<sup>29</sup> x-7 virus contains the HA of AO, the CF of AO and A2, and the neuraminidase of A2. In gel electrophoresis, it shows three peptides, two of which come from AO and one from A2. Other properties are also hybrid between these two viruses.

There are also natural occurrences of hybrid virus formation. The virus involved in the 1918 human pandemic contained swine antigens,<sup>30</sup> and may, therefore, have been a recombinant between swine and human viruses. Also, some viruses which have been isolated from turkeys and ducks have the same neuraminidase as a human strain.<sup>29</sup>

In human epidemics, constant antigenic drift among influenza viruses has been observed. AO was the predominant virus until 1950, A1 from 1951 to 1957, A2 from 1957 to 1968. The Hong Kong strain (1968) is a strong variant of A2 and might possibly be classified as A3 (Pereira, personal communication), *i.e.*, its hemagglutinin is antigenically different from that of A2 (1957), but contains the neuraminidase of A2 (1957).

*Other Changes:* In addition to the foregoing genetic changes, there may also be other changes on the surface of the virion which affect its epidemiologic behavior. There are host-induced changes which depend on the type of cell in which the virus multiplies. These changes may be brought about by changes in the membrane structure of the virus.<sup>27,31</sup> This is important because influenza virus appears to infect cells by fusing its outer membrane with the cell surface and releasing its genetic material inside the cell cytoplasm.<sup>32</sup> Thus, any change which would affect cell fusion, such as a change in the lipoprotein of the virus surface, would affect penetration and infection by influenza virus.

Influenza viruses are undergoing constant antigenic drift with the appearance of a new virus every eight to ten years. Such an antigenic variation seems to be unique for influenza viruses and cannot be explained by mutation or true recombination. This unusual behavior of influenza virus is possible because the viral genome consists of multiple subgenomic fragments or RNA molecules. A new hybrid virus can be formed by exchange of one or more RNA molecules when two viruses infect the same host. The large variety of influenza strains which infect different animals and the many minor mutations which constantly change the viral genome provide a large pool of heterogeneous genomes which may contribute to the formation of new hybrid virions. It is, therefore, impossible to predict the nature of future hybrid viruses which can potentially cause new epidemics.

### Epidemiology in Los Angeles

DR. ST. GEME: We would be remiss if we failed to place our story about influenza-1968 in its appropriate perspective as one relating the events of only a small portion of an explosive, widespread epidemic.

DR. KAMEI: \* The influenza surveillance methods employed to monitor the 1968 epidemic in Los Angeles County depended upon reports on absences from selected elementary, secondary schools and from available private industries. Information was also studied from hospitals in which patients with upper respiratory illnesses were treated.

Between November 15 and November 20 reports of influenza-like activity were received and investigated by the Los Angeles County Health Department. Throat cultures obtained from these patients revealed the presence of influenza A2 virus, Hong Kong variant.

The first indications of county-wide influenza activity were noted during the week ended December 7, 1968. The peak of the epidemic was noted during the week ended December 28, 1968. By the end of January 1969 all epidemiologic measurements were back to pre-epidemic levels.

Pneumonia-influenza deaths rose sharply during the first week of January. Statistically significant excess "pneumonia-influenza" deaths followed the estimated peak of the epidemic by three weeks.

\*Ichiro Kamei, M.D., Chief, Acute Communicable Disease Control Division, County of Los Angeles Health Department.



The estimated excess mortality due to "pneumonia-influenza" during earlier influenza epidemics in the United States, e.g., 1957, 1958, 1960 and 1963, was approximately 12,000, 6,000, 11,000 and 11,000, respectively. During the 1960s, the estimated case-fatality rates nationwide were roughly six or seven per 100,000 population. This rate is essentially the same for the 1968 Hong Kong flu epidemic experience in Los Angeles County.

The maternal mortality rate in Los Angeles County has not changed significantly over the past 15 or 20 years. We do not have information on the maternal deaths associated with the Hong Kong flu. No conclusion can be made regarding the significance of influenza on maternal mortality.

DR. ST. GEME: We will conclude with a brief review of the potential effect of influenza virus infection on the pregnant woman, the encounter which initiated in so devastating a fashion our extensive discussion in this conference.

DR. BRADLEY: With respect to the question of spontaneous abortions occurring in pregnancy complicated by influenza, the available information is indeed sparse. Most investigators are of the opinion that in early pregnancies complicated by influenza there is a higher incidence of spontaneous first trimester abortions. However, this is not a universal view. Whether or not there occurs an increased likelihood of congenital malformation is also debatable. Reports by Saxen<sup>33</sup> in Helsinki, Coffey and Jessop<sup>34</sup> in Northern Ireland, and Hardy<sup>35</sup> in Baltimore would suggest that this is the case.

The overall mortality rate during the 1918 epidemic was approximately 40 percent, as previously mentioned. Harris<sup>36</sup> in 1919 reviewed 1,350 cases of influenza complicating pregnancy occurring in Maryland. In 50 percent of the cases pneumonia developed and 50 percent of these patients died. The statement has been made that this high mortality rate was very likely due to bacterial superinfection in the pre-antibiotic era. It is interesting to note that in Greenberg's<sup>37</sup> review of 216 influenza deaths occurring in New York City in 1957, 10 percent occurred in pregnant females; one-half of the women aged 15 to 45 who died were pregnant. Freeman and Barno<sup>38</sup> in 1959 reported the influenza deaths occurring in Minnesota. In this series also, half of the females aged 15 to 45 who died were pregnant. One may

summarize the problem of influenza and pregnancy by saying that during an epidemic the pregnant patient is somewhat more likely to contract this infection, has a greater tendency toward spontaneous abortion and stillbirth, is somewhat more likely to have her fetus affected by congenital malformation, and is in great risk of death should pneumonia develop.

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### AUSCULTATION OF VENTILATORY FUNCTION

"Remember in testing dynamic ventilatory function that you can get a great deal of information at the bedside with that archaic instrument, the stethoscope, especially in determining the mechanism of airway obstruction. One can assess the quality and uniformity of air entry and air exchange, the presence or absence of wheezing, its pitch, and the effect upon wheezing and air exchange of having the patient cough or of having him breathe after the spray of a bronchodilator aerosol. Most important (and I urge each of you to incorporate this into your examination of the patient with pulmonary disease), listen to the patient during quiet breathing and then have him do a maximum ventilation maneuver — have him hyperventilate — and watch and listen to what happens to the air entry and to the sounds of air movement and wheezing in his chest. This is the shouldering phenomenon obtained from a simple spirogram. You can get this kind of information by having a patient with chronic obstructive airway disease hyperventilate without any kind of equipment. He will rapidly begin to breathe out and you'll hear a little bit of an air exchange as if he hits an obstruction; you see him turn red, the veins in his neck stand out, and you don't get any air movement. Or in a tight asthmatic, you may begin to hear high-pitched wheezing whereas if you listen to him during quiet breathing, there is no wheezing at all."

—ASHER MARKS, M.D., Miami

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# Important Advances in Clinical Medicine

## *Epitomes of Progress -- Allergy*

*The Scientific Board of the California Medical Association presents the following inventory of items of progress in Allergy. Each item, in the judgment of a panel of knowledgeable physicians, has recently become reasonably firmly established, both as to scientific fact and important clinical significance. The items are presented in simple epitome and an authoritative reference, both to the item itself and to the subject as a whole is generally given for those who may be unfamiliar with a particular item. The purpose is to assist the busy practitioner, student, research worker or scholar to stay abreast of these items of progress in Allergy which have recently achieved a substantial degree of authoritative acceptance, whether in his own field of special interest or another.*

*The items of progress listed below were selected by the Advisory Panel to the Section on Allergy of the California Medical Association and the summaries were prepared under its direction.*

Reprint requests to: Division of Scientific and Educational Activities, 693 Sutter Street, San Francisco, Ca. 94102

### The House Dust Mite

House dust allergy, long considered the most prevalent form of respiratory tract allergy, has gained new interest through the discovery that skin tests with an extract of a common household mite of the genus *Dermatophagoides* show close correlation with tests to commercial house dust extracts. The dust samples from which the extracts are made show large numbers of mites on microscopic examination in the majority of cases. Inhalation tests with mite extracts and house dust extracts also suggest that a major component, possibly the major component, in house dust allergy is derived from mites.

Such observations, originally made in Holland, have been confirmed by many reports from Great Britain, Japan, the United States and elsewhere.

The mite is regularly found in kapok and cotton lintens in upholstered furnishings such as mattresses and box springs and is cultivated best in media containing human skin scales.

While not yet easily available for skin testing, the likelihood is that mite extract will soon be found routinely on allergists' testing trays. Its place in the treatment of house dust-sensitive patients is yet to be determined.

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## Recent Laboratory Evidence of Benefits From Injection Therapy for Pollinosis

While injection therapy for pollinosis is widespread, scientific proof of efficacy has been difficult to obtain in purely clinical studies because of the subjective nature of symptom reporting and the known beneficial effects of placebo therapy. Recent refinement of the technique of *in vitro* histamine release from peripheral blood leukocytes of allergic persons on exposure to specific allergens provides a means to quantitate and manipulate a process believed to be one necessary step in the development of allergic symptoms *in vivo*.

Grass extract, whole ragweed extract, and the antigen E fraction of ragweed extract have been studied. Following immunotherapy of several months' duration there is significant decrease in the percent of total histamine released by leukocytes on exposure to the corresponding allergen. This leukocyte unresponsiveness parallels a fall in reaginic antibody titer and a rise in blocking antibody levels, and closely correlates with clinical improvement. The profound fall in leukocyte responsiveness cannot be explained solely by the relatively lesser drop in reagin titer; the concomitant rise in serum IgE blocking antibody titer seems to be crucial to clinical improvement.

V. MARINKOVICH, M.D

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## The Use of Disodium Cromoglycate In the Treatment of Asthma

"INTAL®," disodium cromoglycate (DSC), a product of Fisons Pharmaceuticals of England, has been on the market for three years in England, Australia and other countries. It is still under investigation in the United States.

This drug, an odorless white powder, is used in the prevention of asthma attacks by a mechanism

not available in other forms of medication—it is not a bronchodilator, an anti-inflammatory agent, steroid, or antihistamine, but prevents the release of histamine from mast cells.

Twenty milligrams of the drug is given by powder inhalation in a special "spinhaler" four times a day. Most clinical trials have reported unequivocal subjective benefit in one-third to one-half of patients with extrinsic asthma. Many patients have been able to decrease their regular doses of bronchodilators, steroids and sympathomimetic inhalers. There have been no reported serious side effects.

Exercise-induced asthma and inhalation-challenge asthma can also be successfully blocked by previous treatment with DSC.

The drug is not effective for treating the acute attack of asthma.

JAMES R. CRISP, M.D.

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## Immunoglobulin E in Allergic Disease

Reaginic antibodies responsible for immediate type hypersensitivity reactions including classical allergic symptoms have been assigned to a new class of immunoglobulin designated IgE or  $\gamma$ E. Present in everyone from shortly after birth, the serum concentrations of IgE slowly increase throughout life. Normal adult sera have a mean level of 0.3 micrograms per ml with a range of 0.1 to 1.4.

Atopic persons have a tendency to higher levels when compared with age-matched controls, but there is considerable overlap. Serum concentrations have been shown to be elevated in a variety of conditions without concomitant allergic symptoms. These include visceral larva migrans syndrome, ascariis infestation and, in lower frequency, celiac disease and Laennec's cirrhosis.

Allergic symptoms are most likely due to the synthesis of IgE antibodies specific for prevalent



allergens, rather than to a heightened capacity for IgE synthesis. The conditions which lead to specific IgE antibody synthesis remain obscure, but definition of the IgE class of immunoglobulin promises to aid research on this question.

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### The Use of Immune Serum Globulin (Gamma Globulin)

Immune serum globulin or pooled human gamma globulin (Cohn Fraction II) is of proved value in the prophylaxis of measles and infectious hepatitis and in the therapy and prophylaxis of infections in hypogammaglobulinemia. A dose of 0.02 ml per kg of body weight is usually sufficient for the prophylaxis of measles or infectious hepatitis.

Although the administration of immune serum globulin is of proved value in well-documented hypogammaglobulinemias, before recommending its use in borderline or mild hypogammaglobulinemia, a deficiency in antibody production should be clearly demonstrated. This can most readily be done by showing a lack of antibody response to two different antigens such as diphtheria and tetanus toxoids. Defective antibody production should also be demonstrated before immune serum globulin is given to patients with dysgammaglobulinemias unless very low levels of  $\gamma$ G are present (less than 200 mg per 100 ml in young children or under 400 mg per 100 ml in older children and adults). The recommended dose for therapy and prophylaxis of antibody deficiency states is 1.5 ml per kg initially, followed by 0.66 ml per kg every 3 to 4 weeks.

Immune serum globulin may also be given (although its value has not clearly been shown) in an effort to prevent rubella in the first trimester of pregnancy, in the prevention of chicken pox in high risk patients such as children who are receiving steroid therapy or who have leukemia, and in the prophylaxis of serum hepatitis in high risk patients receiving blood transfusions. Patients at high risk for serum hepatitis include those with debilitating or chronic illnesses or anyone

who receives blood or blood products strongly suspected or known to be infectious.

Hyperimmune serum globulins obtained from hyperimmunized or convalescing persons may be of use for specific diseases in which ordinary immune serum globulin is of doubtful value. They are available for mumps, pertussis, tetanus, and vaccinia. No prophylaxis is indicated for prepubertal children exposed to mumps, but mumps immune globulin may be used in exposed susceptible postpubertal males. Its value has not been well documented by controlled studies. The prompt administration of live attenuated mumps virus vaccine following exposure is preferable to giving mumps immune globulin.

Pertussis immune serum globulin may be used in doses of 1.5 ml in exposed infants under two years of age who have not been vaccinated. It may be repeated in five days if desired by the clinician.

Tetanus immune globulin should be used for unimmunized individuals with crushing injuries, burns, penetrating wounds and the like, in those who have had no tetanus toxoid injections for many years. Human tetanus immune globulin is given in a dose of 250 to 500 units intramuscularly. If human antitoxin is not available, equine tetanus antitoxin in a dose of 3,000 to 10,000 units may be given after testing for horse serum sensitivity. Human immune globulin is preferable in all instances in which it is obtainable.

Vaccinia immune globulin is useful in the prophylaxis and treatment of vaccinia of the eye, eczema vaccinatum, severe generalized vaccinia, or vaccinia necrosum. It may also be used in children who have extensive skin lesions including eczema, burns or impetigo and are accidentally exposed to vaccinia. Vaccinia immune globulin is not of value in the therapy of normal vaccination reactions and post vaccinal encephalitis, or for treatment of conditions such as chicken pox and herpes zoster. The prophylactic dose is 0.3 ml per kg of body weight.

There is no acceptable evidence that immune serum globulin is of value in the therapy of asthma or of recurrent infections not associated with documented hypogammaglobulinemia or a proved disorder in antibody production.

DOUGLAS C. HEINER, M.D.

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## Immunoglobulin IgA

Serum IgA is absent at birth but appears at about four weeks of age and by the age of 12 months is near the adult level. The serum values in children range from 49 to 114 mg per 100 ml. Serum IgA has a molecular weight of 165,000 and had a 7S sedimentation coefficient. Secretory IgA is similar to serum IgA. It is present in secretions in pairs linked to a "secretory piece." This combination is thought to be made locally in mucous membranes. "Secretory piece" is a G-globulin with a molecular weight of 50,000. Theories suggest that local antibodies, especially IgA, are important in the resistance to respiratory tract infections and play an important role in gastrointestinal and genitourinary tracts. Serum IgA is present in parotid, bronchial, small intestinal, prostatic and vaginal secretions as well as in colostrum, amniotic and lachrymal fluids.

M. MILLMAN, M.D.

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## New Information on Allergic Rhinitis

Important information on the mechanism producing allergic nasal symptoms has emerged from studies made possible by the development of an instrument for measuring the effective nasal airway. These measurements have been obtained in conjunction with a method permitting control of the rate and amount of pollen administered intranasally. Objective responses have been measured quantitatively, under controlled conditions, before, during and after therapy.

The parameters of the nonspecific primary effect have been defined. An increase in reactivity of the nasal mucus membrane following repeated exposure to pollen is only slowly reversible over a period of days to weeks. By administering pollen to one nostril, this was shown to be a local effect rather than systemic. This resulted in unilateral priming and allergic rhinitis in the challenged nostril only.

Priming has been shown to be nonspecific in that hyperreactivity induced by one pollen (to which the patient is sensitive) results in a pronounced increase in sensitivity to a low dosage of another, unrelated pollen. This finding reemphasizes the importance of considering "the total allergic load" when evaluating allergic reactions.

Recently attempts to suppress the nasal membrane's allergic reaction to pollen by a nasal spray containing blocking antibody has had some success. Thus, it may be possible to treat patients with allergic rhinitis by first stimulating blocking antibody synthesis by conventional injection of antigen and then using the serum as a source of blocking antibody for use in nasal sprays.

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## Hypersensitivity to Organic Dusts

An increasing number of organic dusts have been shown to produce allergic lung diseases similar to farmer's lung. Persons exposed develop precipitins which react specifically with antigens in the dust. Inhalation of the dust apparently incites an arthus reaction in the lung. Alveolitis and pulmonary fibrosis follow. About half the patients have repeated bouts of fever and pneumonitis. The remainder have a slowly progressive course, with cough, weight loss and pulmonary infiltration. Coexisting reaginic (IgE-mediated) allergy, as revealed by immediate wheal and erythema skin tests, may modify the symptom pattern to one of asthma plus pulmonary infiltration.

A partial list of these diseases and the dusts which cause them: *Farmer's lung*—moldy overheated hay; *bagassosis*—moldy sugarcane bagasse; *maple bark*, *sequoia bark*, *oak bark pneumonitis*—moldy bark; *bird breeder's lung*—pigeon and budgerigar droppings. New diseases of this type are being found. The newest is *washing powder*



*worker's lung*—due to the enzymes from *B. subtilis* in washing powders.

Diagnosis is made by history, the presence of precipitins in the serum and a delayed, arthus-like reaction on skin testing. Treatment with adrenal corticosteroids seems to help, but avoidance of the offending dust is the most effective therapy.

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### The Beta-Adrenergic Blockade Hypothesis of Asthma

Beta-adrenergic stimulators, such as epinephrine and isoproterenol, relax bronchial smooth muscle, decrease glandular secretion, constrict blood vessels and also alleviate asthma. Beta-adrenergic blockers, such as propranolol (Inderal®), have the opposite effects. These observations have led to the theory that the basic defect in asthma is a partial  $\beta$ -adrenergic blockade. The causes of this postulated blockade might include hereditary influences and infections. Although as yet unproven, this theory has stimulated much new thought and experimental work on asthma. The theory would explain the diminishing therapeutic effectiveness of beta stimulators in patients with long-standing asthma and the subnormal cardiovascular and metabolic responses of asthmatic patients to  $\beta$ -adrenergic stimulators. On the other hand, normal subjects given propranolol do not develop the bronchial sensitivity so characteristic of asthma, and exercise-induced asthma seems to occur via mechanisms other than  $\beta$ -adrenergic blockade. Additionally, new information suggests that decreased  $\beta$ -adrenergic (epinephrine) secretion by asthmatics during stress may be related to their bronchial hyperreactivity.

GILDON N. BEALL, M.D.

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### Hereditary Angio-Edema

Urticaria and angio-edema are common complaints. Foods, inhalants, insect stings, intestinal parasites and medications are frequent causes. There are other factors, some simple and some complex, such as: solar, thermal, pressure, infections and neoplasms.

Thompson gave an excellent review of these mechanisms which produce lesions by release of histamine.

Donaldson and Evans showed that patients with hereditary angio-edema are lacking alpha globulin which inhibits the esterase activity of complement.

Patients with hereditary urticaria and angio-edema need a confirmed laboratory diagnosis, as surveys show a 28 percent death rate from laryngeal edema. Antihistamines and steroids reduce attacks, but an adequate airway with epinephrine or isoproterenol are necessary in life-threatening attacks.

JOHN S. O'TOOLE, M.D.

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Thorvaldsson SE, Sedlack RE, Gleich GJ, et al: Angioneurotic edema and deficiency of C:1 esterase inhibitor in a 61-year-old woman. *Ann Intern Med* 71:355-357, 1969

### Newer Trends in Corticosteroid Therapy

A dosage schedule for corticosteroids involving the administration of the total 24-hour dosage in a single dose every other day rather than in divided doses during this same period has been fairly well accepted. Evidence of satisfactory efficacy and of substantially reduced side effects with long-term alternate-day therapy has been well documented.

It has been recommended that any patient requiring prolonged corticosteroid administration be given a trial of alternate-day therapy before being committed to a long term daily corticosteroid regime. Patients who require daily therapy at the onset to control symptoms should have regular attempts made to switch to an alternate-day regime.



Evidence has been reported that ACTH does not hasten the recovery of the normal pituitary-adrenal function in patients who experienced prolonged steroid-induced pituitary-adrenal suppression.

Prolonged ACTH therapy has been shown to produce antibodies to ACTH that cross-react with endogenous ACTH, binding it in the circulation in inactive form.

LEO N. MELEYCO, M.D.

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- Fleischer N, Abe K, Liddle GW, et al: ACTH antibodies in patients receiving depot porcine ACTH to hasten recovery from pituitary-adrenal suppression. *J Clin Invest* 46:196-204, 1967

### The Management of Respiratory Failure In Childhood Status Asthmaticus

In the management of 30 episodes, the criteria for respiratory failure consisted of the following clinical signs: decreased or absent inspiratory breath sounds, severe inspiratory retractions and use of accessory muscles, cyanosis in 40 percent oxygen, depressed level of consciousness and poor skeletal muscle tone.

The technique evolved included tracheal intubation followed by general anesthesia and manual ventilation, mechanically assisted ventilation with a pressure-flow cycled ventilator under heavy sedation, neuromuscular blockade with d-tubocurarine and light sedation and controlled ventilation with the Emerson volume regulated respirator.

Blood gases were determined frequently. There were 18 complications, including one death. The investigators reported an experienced, constantly available team is necessary.

NADIA SOROKOWSKI, M.D.

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### Hypoxia in Asthmatic Attacks

The dehydrated adrenalin-fast patient is acutely ill and needs intensive care management. All such patients have hypoxia, and arterial blood gas measurements are essential in control to prevent respiratory failure.

A  $p\text{CO}_2$  of 60 or above is an indication of the need for assisted ventilation by means of a Bennett, Bird or Emerson machine with the use of either a laryngeal catheter or tracheotomy. A  $p\text{O}_2$  below 50 increases danger of cardiac arrest. Oxygen can be given at a low flow rate as frequent  $p\text{CO}_2$  determinations are done.

Steroids in large doses and antibiotics are also essential to proper management.

JOHN S. O'TOOLE, M.D.

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### Aspirin Sensitivity

Untoward reactions to aspirin take two forms: (a) appearance of the expected symptoms of over-dosage from normally tolerated amounts, and (b) the more serious allergic or anaphylactic type of sensitivity. In children, sensitivity usually appears in the form of urticaria, angio-edema or a macular eruption, occasionally with purpura. Sensitivity in adults tends to appear in middle life—in my experience, most often in women between 35 and 45 years of age. The typical patient has suffered from a vasomotor rhinitis leading to nasal polyposis. Only 10 percent show evidence of atopy, or familial allergy. An "intrinsic" (non-allergic) asthma may precede or coincide with the onset of aspirin sensitivity. The asthma usually follows a respiratory infection, but may appear suddenly after nasal operations. Once aspirin sensitivity is established, even minute amounts of aspirin can produce alarming or even fatal bronchospasm.

The sensitivity is highly specific: among the salicylates only acetyl salicylic acid provokes the reaction. However, cross reactions regularly occur

with indomethacin, aminopyrine and antipyrine; to a lesser extent with FD+C Yellow No. 5 food coloring.

Acetyl salicylic acid appears not to be an antigen or antigenic determinant in the usual sense, and no specific antibody has ever been found. Samter and Beers postulated that in these patients aspirin potentiates rather than inhibits the activity of the kinin receptors in skin, nasal membranes and bronchioles.

The asthma that accompanies aspirin sensitivity is usually difficult to control, and can lead more or less rapidly to decided pulmonary insufficiency. The nasal polyps recur regularly after removal. Generally the best method of handling the aspirin sensitivity-asthma-nasal polyposis triad consists of prompt and vigorous treatment of respiratory infections with broad spectrum antibiotics, systematic use of oral bronchodilators and, from time to time, vasoconstrictor-antihistamine combinations by mouth. Small amounts of prednisone or prednisolone given daily or intermittently can be remarkably effective for long periods.

In patients with demonstrable atopic allergy, careful immunotherapy can reduce the frequency and severity of the asthma, and retard (if not prevent) regrowth of nasal polyps.

WALTER R. MACLAREN, M.D.

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Kaplan MJ, Lanoff G: Aspirin allergy in children. *Dome Laboratories Allergy Newsletter* 6, 1:151, 1970

### Pathology of Bronchial Obstruction In Asthma

Bronchial asthma is a chronic disease characterized by paroxysmal bronchial obstruction and ventilatory insufficiency. Bronchi and bronchioles are the seat of the essential pathological changes. There is mucosal edema, hypersecretion of a thick tenacious mucus and smooth muscle contractions. Extrinsic asthma occurs in individuals who have been sensitized followed by a reexposure of the specific antigen. An antigen-antibody reaction occurs in a lung followed by release of histamine, slow-reacting substance of anaphylaxis, bradykinin, and other substances which are pharmacologically active. The action of these substances on mucous glands, smooth muscle and blood

vessels presumably produces the asthma. The obstruction to airflow caused by mucosal edema, mucus hypersecretion and smooth muscle spasm results in a decided narrowing of the bronchial tree.

In the severe forms the obstruction causes hypoxemia, hypercapnia, cor pulmonale and finally death from widespread obstruction of the airways by inspissated mucus. The mucus is thick and stringy, causes coughing and contributes to the wheezing and the shortness of breath. As time goes on the smooth muscle becomes thickened, the mucous glands become prominent, and distended mucus-engorged goblet cells are common in the bronchiolar wall. There is thickening of the basement membrane. At autopsy a cellular infiltration is found that consists mainly of eosinophils and frequently plasma cells. Additional pulmonary lesions which are due to complications from the above are chronic bronchitis, atelectasis and peribronchial and pulmonary fibrosis.

M. MILLMAN, M.D.

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Liebow AA, Smith DE: *The Lung*. Baltimore, Williams and Wilkins Co., 1968, pp 105-304

### Life-Threatening Asthma

Errors which may contribute to respiratory failure in the treatment of life-threatening asthma are improper use of sedation or oxygen, or inadequate steroid administration.

Decreasing wheezing by auscultation despite increasing dyspnea is an ominous sign of impending respiratory failure. Therapy should include antiasthmatic medication, antibiotics and proper use of oxygen and steroids. The decision as to when to start assisted ventilation can be made on the basis of blood gas values and clinical judgment. If the  $p\text{CO}_2$  is rising while the  $p\text{O}_2$  and pH are falling despite active treatment, assisted ventilation may be needed. Three patients were ventilated by use of intermittent positive pressure breathing and five required a volume respirator.

NADIA SOROKOWSKI, M.D.

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## The Allergic Tension-Fatigue Syndrome

Allergic (toxemia) tension-fatigue syndrome occurs commonly and is frequently unrecognized. It occurs in both children and adults, is usually due to food allergy, most commonly to milk, chocolate, wheat or corn, is more manifest in winter and may subside in summer for reasons that are obscure. Inhalant allergy is a less frequent cause, usually suspected because of seasonal coincidence.

Symptoms include easy fatigability, respiratory tract allergy, gastrointestinal disorders, headache, tenseness, irritability, pallor, musculoskeletal aching and decreased cerebration, but any organ

system may be involved. One or more of these manifestations may be present.

A detailed history and elimination diet trial for a period of three to six weeks are required for diagnosis. Skin tests are seldom helpful. Allergy must be considered in a patient presenting these symptoms.

E. JAMES YOUNG, M.D.

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# Relevance in Medical Education

## Some Thoughts from a Forum

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*For the past several months the editors of CALIFORNIA MEDICINE have conducted a forum in this journal on "Relevance for Today and Tomorrow in Medical Education." The participants were from widely different backgrounds and represented many points of view. This statement is a distillate from published and unpublished material contributed to the forum. If it proves useful to any who may be concerned with new developments in medical education it will have served its purpose.*

MEDICAL EDUCATION is embarked upon a process of fundamental change. The traditional approach, hardly questioned for decades, is now being seriously challenged. The pressures are not so much from medical school faculties, who have been rearranging and adding to the curriculum for years, as they are from forces outside the faculties. The truly significant pressures for change have come from students, from practicing physicians who have pleaded for less emphasis on research and more on community medicine and family practice, from government which grants or withholds funds according to its often bureaucratic interpretation of the public interest, and most recently from the public itself which clearly considers that health care in this nation is unsatisfactory for 1970, let alone for 1980, 1990 or the year 2000. These pressures have brought about vigorous ferment in medical education. It is certain that there will be new directions, even an exciting new order, but it is not certain just what these will be. This distillate from the forum that has been presented in these pages seeks to probe what these may be.

### Relevance

The word *relevance* was deliberately chosen as the key word in the title for a forum on medical education, and the editors believe that it was a happy choice. For one thing it is currently an "in" term, one likely to attract interest and attention, and this proved to be the case. But more importantly it caused the forum participants to reveal a broad spectrum of views with respect to the purposes of medical education.

A review of the comments indicates that the art and science of caring for the sick were central to medical education and it was generally (though often tacitly) recognized that medicine in the future must rest firmly on the base of biologic science as this has been and continues to be developed. But for almost all, relevance in medical education has come to mean much more than this. Many equated relevance with words such as *useful, practical, action*, and even *reform*. Relevance was also equated, by one contributor, with a "learning process which should lead to a complete understanding of life and living," and in another's view with achieving a knowledge of the processes of disease. Still others identified relevance in medical education strongly with new

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technology for health care delivery, the right of every citizen to have access to high quality services, disease prevention, promotion of a healthier environment and a healthier society, and one cogently pointed out the important relevance of sources of income to what goes on in medical schools and in medical education. Student views were summarized by one experienced educator to say "give us practical training," "help us acquire knowledge, skills and attitudes that will enable us to serve all the health needs of society more completely and more humanely than we see our elders doing," "let us be more involved in our own education—allow us to help decide what we need to learn and especially how we go about it," "give us opportunity to prove for ourselves that the science you want us to learn is relevant." Another interprets student demands for relevance to mean less basic science, earlier clinical medicine, more preventive medicine, more mass medicine, an increased voice in administration and a demand for instant investment of resources in a frontal attack on problems of black and poor. Other contributors drew attention to the need to learn how to avoid obsolescence of one's medical education with changing science and changing society, and they pointed also to the very practical relevance of health education and health problems in other parts of the world as they might influence what is being done or could be done in medical education in this nation.

It is suggested that the message which comes through from the above is (1) that medical education is now becoming an entirely new endeavor; (2) that the role of the professional, particularly the medical professional, needs new definition in modern society; and (3) perhaps most importantly, that there is no clear consensus or agreement as to what today's and tomorrow's physician will be or should be doing. Lacking such a consensus or agreement, then, there can be no precise determination of purpose or relevance in medical education.

### A New Ball Game

When the comments of the forum participants are considered in their totality, it is evident that medical education should now be somewhat redesigned to prepare students to play in a new and considerably different ball game. For example, the aim of the game is no longer simply to restore health to an ill person. This remains an important

and central purpose but others have been added. In fact a kind of continuum of concern is becoming apparent, which can be seen to run the gamut from restoring health to the sick and injured, to heavy emphasis on prevention of illness and health maintenance, to maintaining a healthy state in the biologic ecosystem which is profoundly influenced by the behavior and acts of man; and before long one may expect the present interest in human genetics and population control to expand into a public concern with the health and improvement of the human species itself.

Besides these new aims for the game, the health care ball park will be different. Again a new continuum may be seen developing. The former concern only with sick, injured and disturbed patients, has already expanded to include persons not ill, and is rapidly moving into the field of health care delivery and community health. More recently, and with almost explosive suddenness, the importance of human ecology has just begun to burst upon the human consciousness. The full implications of human nature and human behavior, in health and disease, to the well-being of human society and the earth environment are yet to be appreciated or even studied.

And this new ball game has some new rules which will have to be learned. Fundamentally there is no longer enough of everything for everybody and it is unlikely that there ever can be from now on, at least for the foreseeable future. Resources of land, sea, air, money, doctors, health personnel and facilities have already fallen short of demands and expectations and it is unlikely they will ever catch up. If the new aims in health care are to be achieved, there will need to be new concepts for such things as rights, needs, eligibility, access, quality, efficiency and effectiveness, and new rules will have to be developed for this new ball game.

### A Professional's Responsibility

One thoughtful contributor quoted Maxwell\* who, in discussing students' views of relevance, stated, "There is no objective relevance—the relevance of a topic, course, curriculum or the entire educational experience (in their view) can only be judged by the individual in terms of *his* view of society, *his* goals, *his* expectations." Another participant stated, "The scope and responsibility

\*Maxwell WD: Some dimensions of relevance. Bull Amer Assoc Univ Professors, 55:337-341, 1969

of medicine as defined jointly with society are the basis for judging the relevance of medical education." These two statements seem to raise important issues with respect to the responsibility of a professional in society. Is this responsibility primarily to himself, to his profession or to society—or how much to each of these? These questions are relevant to medical education.

The responsibility of medicine as a profession was clearly a strong undercurrent of the forum. Currently there is much to suggest that the principal professions—law, medicine, education and even the clergy—have been too much turned in upon themselves and too little concerned with problems of society or with applying their special knowledge and expertise in guiding the efforts of society to solve problems of an increasingly technologic and interdependent nature. Each of the professions mentioned can be challenged and faulted on this score. Whatever the cause, until very recently these professionals gave their social responsibilities short shrift indeed. For medical education the cumulative effect of 25 years of generous government funding for research and closer association with university settings is not to be discounted. There is little doubt that during this time medical education has become more academic and less professional in character. Society has responded to this professional apathy toward its needs by turning, in a kind of desperation, to the consumer in the hope that somehow his innate wisdom will find the answers which the professionals had failed to seek.

There is much in the forum to suggest the beginnings of a greater recognition of the professional responsibility of physicians and medicine to society as a whole. For today's medical student, considerably the product of the "free speech" movement and modern existentialist thought, the problem is often whether his personal commitment is internal, to himself, or external to the society he has chosen to serve. The professions, particularly medicine, and the medical schools and universities are also being pressured to examine the relation between external responsibilities and internal satisfactions. Obviously the modern professional must satisfy both his internal needs and his external responsibilities. The same is true of education for the professions.

A number of comments in the forum are particularly pertinent. In an unpublished item, a distinc-

tion was made between science and professional expertise. It was suggested that the scientist and his science are generally independent of time and place, while the professional is involved in making professional decisions which are of necessity relevant to time and place. More specifically there were calls for medical education to become more concerned with what medical students can do and less with what they know, calls for educational designs better to fit the student for practice in tomorrow's world and better to respond to the scientific, economic, sociologic and political, as well as medical, needs of the American public. In an important caveat it was noted that medical centers cannot respond to every demand made upon them and that in their zeal for reform and preparation for tomorrow they must not fail to meet today's obligations.

### The "Compleat Physician" — A Composite

A medical student participating in the forum stated: "The problem of relevancy in medical education will only be solved when the medical schools recognize that their primary mission is to educate physicians who are capable of meeting the health care problems, not only of today, but those which will arise in the future."

This succinctly states the problem. It is a large order and a difficult one to find a way to fill. However, if one plots the continuum of health care mentioned previously against those attributes, tools and skills which many of the participants stated physicians should have or acquire in a relevant medical education, there seems to emerge a crude framework or composite of what the "compleat physician" might indeed be. This is set forth in Chart 1. It will be noted that each of the physician attributes listed applies to each of the elements in the continuum of health care. Time and space do not permit discussion of all of these elements and attributes. Each was alluded to in some way by one or another of the forum participants. The framework could be filled out more completely with definition of what is encompassed in each of the attributes and elements and what is to be found in each of the boxes in the chart where they interface. While no physician can be all things at all times, the composite of the whole profession might be expected to comprise the "compleat physician."



Chart 1.—The "Compleat Physician"—A Composite

← CONTINUUM OF HEALTH CARE →

	<i>Sick and Injured Patients</i>	<i>Health Care of Persons Not Ill</i>	<i>Health Care Delivery</i>	<i>Community Health Care</i>	<i>Environmental Health Care</i>	<i>Species Health Care</i>
↑						
Motivation						
Health Science						
Craft Skills						
Ethics Attitudes						
Lifelong Scholarship						
Skills for Social Action						
↓						

### SOME SUGGESTIONS FOR GREATER RELEVANCE IN MEDICAL EDUCATION

Given the reality of a new ball game in health care, a beginning new recognition of great responsibility for professionals in modern society, and a developing new concept of the "compleat physician," it now becomes possible to examine some of the characteristics medical education should have or acquire to be or become relevant for today and tomorrow. The participants in the forum had many suggestions which seem worthy of serious consideration.

#### *Some General Principles*

A number of general principles were stated. These are a few which seem particularly important. Medical education must rest firmly upon the biomedical base which has begun to develop in the last 25 years. Medical education is a continuum which starts in preparation for medical school and extends through formal medical edu-

cation to include a lifetime of learning. There should be clearer definition of what a physician needs to know and of what he should be able to do. The learner should be able to acquire the tools to practice his profession in the process of his education.

Deserving of particular emphasis is the fundamental fact that the basic knowledge and discipline of the physician will always lie in the care of the sick. If a comparison with a tree may be made, this is the root which has to sustain everything else the physician ever does or may do in society. However from this root, and from its strong trunk of basic knowledge and skills grow many branches of scholarship and practice and their number is increasing all the time. Medical education must somehow see that the root is firmly planted and well nourished. It must see to it that the trunk be strong and also that there be stimulus and support for the growth of many branches. Finally it must instill a capability and determination to adapt and adjust to an ever changing science and environment.

### *Some Tools Which Should Be Acquired*

Just as caring for the sick is the root of the physician's professional tree of life, so the tools of his profession are its trunk. These tools, as they are identified by the participants in the forum, are listed as the "attributes" of the doctor in the diagram of the "compleat physician" (Chart 1).

*Motivation* was recognized as greatly in need of more study and understanding. It is not easily separated from incentives either in education or in professional practice. Motivation in medical education was considered in terms of personal fulfillment, service to patients, service to humanity and lifelong learning to understand and to respond to change.

*Science* was discussed not only in terms of traditional medical science, but in terms of social science, and such things as ecology, computer and information science, systems analysis, cybernetics and social engineering.

*Craft skills*, in one context or another, were particularly emphasized by the participants in connection with words such as "practical" and "useful." The scope of suggestions went far beyond the care of the sick and health maintenance to include skills to cope with health care delivery systems, health team structure and function, problems in community health, environmental health and ecology, and even the health of the human species throughout the world now and in the future.

*Ethics and attitudes* were seen as becoming increasingly important tools for physicians who will be frequently called upon to participate in both medical and social decisions of ethical and moral character. It was noted that the question now is less often *can* something be done and more often *ought* it be done. Philosophy and cultural values thus are seen as becoming more and more relevant to many of the roles the physician will play in practice.

*Lifelong learning* or continuing education received considerable emphasis from several participants. It was suggested that not only motivation, but skills and habit patterns for lifelong learning be made a very integral part of medical education at all levels, beginning with particular emphasis in medical school, and that the subject matter include changes in both science and society.

*Technology for social action* was thought by

several to be an appropriate and necessary part of medical education today. The expressed need was for skills which will enable physicians to bring about changes in medicine or society or both when such changes are necessary for the health and well-being of patients or of people. Several contributors felt that tools for social action should be part of a modern physician's armamentarium.

### *Education for Practice*

The forum suggests that practice for the composite "compleat physician" extends all the way across the continuum of health care from care of a sick patient to promoting the health and betterment of the human species throughout the world. If the root of the professional tree is the care of the sick, and the trunk the attributes or tools of the physician, then the branches are to be found in general or specialized practice distributed along this continuum. Specialization, including family practice, already exists for the care of ill patients. It is needed and already beginning to occur elsewhere along this whole continuum of health care. Several participants in the forum expressed the view that medical students should have the same kind of direct contact experience with health maintenance programs, various types of health care delivery systems, community health and environmental health that they will have with the specialties which are directly concerned with patient care. One participant, particularly experienced in international health, pointed out the advantages, to both students and faculty, of an educational experience overseas. It is quite apparent that these kinds of student experiences are increasingly being considered relevant to medical education not only by students but by many practitioners and educators as well.

### *On Changing the Educational System*

A number of participants in the forum suggested major alterations in the present system of medical education. One proposed that there be one kind of school to train "humanists or family physicians" and another to train the "superspecialist, theorist or research academician." Two more participants suggested ways of teaching basic sciences outside of medical schools and in this way expanding the capacity of medical schools to handle more students with a greater breadth of educational experiences including exposure to

more kinds of professional activities, and perhaps accomplish this in a shorter period of time overall. Suggestions such as these appear to merit consideration and study. Nor are they unique to this forum. Many schools are already developing diverse "tracks" leading toward various career goals in medicine. If the suggestion that the basic sciences be taught elsewhere than in medical school were to receive some kind of endorsement, then question arises as to what is the core subject matter which should be taught to all medical students in all medical schools, or what is it that makes a physician a physician.

No participant in the forum addressed himself to this essential question. One suspects the answer might have something to do with the common root of every physician's professional activity, the care of the sick. In its simplest form this core material might deal with the application of the basic sciences already learned in medical school or elsewhere to medicine, and would assume that these include not only the traditional biologic sciences but some of the other disciplines which have been mentioned previously. It should certainly impart the basic knowledge and skills to examine patients and to distinguish between the normal and the abnormal, and between health and disease. Appended to this, and made part of it, might be cultivation of the attributes or basic tools of the physician described above and a substantial amount of direct exposure to the spectrum of physicians' roles and practice in as many different aspects of health care as possible. Such a core program, when linked to completion of one of any number of career "tracks," could produce a variety of specialized physicians, yet each would have in his background a something that made him a physician and not something else.

## CONCLUSION

This summary statement certainly does not include all that is of value in the contributions submitted to this forum on "Relevance for Today and

Tomorrow in Medical Education." For example, the need for more well-trained specialists both in traditional disciplines and in entirely new fields received strong support. A need for better programming of the numbers of various specialists to be produced was expressed. The flexible curriculum, with its individualization of content, duration and emphasis, was warmly praised but at the same time a warning was sounded that such a curriculum may not always add up to a relevant whole. The science of medical education itself was criticized by a non-medical educator of impeccable credentials who found it badly wanting through sins of both omission and commission.

While it is impossible to draw truly defensible conclusions from a forum such as this, the following are suggested:

- If medical education is to be relevant "for today and tomorrow" there is real need for a better consensus with respect to what the physician will be doing in 1980 and later.
- There will be an increasing emphasis on the professional roles of the physician in medical education for the foreseeable future.
- The professional responsibility of the physician, which is rooted in the care of the sick individual, now extends beyond individual health care and even the delivery of health care services, to the problems of human behavior with respect to the immediate environment and the ecosphere.
- Progress toward improving relevance in medical education is well under way. There is much to be defined, much to be determined and much to be done. If this forum has served to draw attention to some of these problems—and perhaps contributed a thought or two to "relevance for today and tomorrow in medical education"—it will have served the purpose which the editors intended.

EDITOR'S NOTE: The editors of this journal wish to express their appreciation to the contributors to this forum for their participation.



## Influenza—Promising New Developments

DR. CHARLES H. STUART-HARRIS in a recent address concluded a tribute to Sir Christopher Andrewes (co-discoverer of the influenza virus) and to Dr. Thomas Francis Jr. (discoverer of influenza B and director of the first influenza vaccine trial) with the following statement: "Thirty-seven years after the discovery of the virus and in spite of all the wealth of knowledge which we possess, it remains a fact that we are still defeated by its prowess." The tragic case of fatal influenza in pregnancy which served as a basis for the UCLA Staff Conference which appears elsewhere in this issue is adequate testimony to the validity of this statement. Nevertheless, progress has been made toward effective control of influenza, and there is reason to be optimistic about the future. A consideration of some current lines of investigation that relate to control is in order.

The most recent contribution to a fundamental understanding of resistance to influenza has been provided by studies on the neuraminidase antigen. There are two major antigens on the surface of influenza virions, the hemagglutinin and neuraminidase. The hemagglutinin spike is known to be the site of attachment to the cell surface for initiation of infection, and neuraminidase has recently been shown to facilitate release of new virus particles from the surface of infected cells. Resistance to infection correlates with the presence and magnitude of the titer of antibody to the hemagglutinin antigen. In contrast, antibody to neuraminidase does not prevent infection but appears to limit the spread within an infected animal as well as spread to other animals. Thus, infected animals with neuraminidase antibody and no hemagglutinin antibody have lower lung virus titers, less pneumonia, and less ability to transmit influenza than animals with neither type of antibody. Knowledge of the epidemiologic factors and clinical manifestations of infection with the Hong Kong variant suggests that similar phenomena occur in man.

In studies of antigenic relatedness between the two major surface antigens, it was found that the Hong Kong variant possesses a unique and new hemagglutinin antigen but that the neuraminidase antigen is similar to that of 1967 strains of type A influenza. This is in contrast to the Asian strain introduced in 1957 in which both antigens were decidedly different from those present in earlier strains (subtype A<sub>1</sub>). In fact, the hemagglutinin

antigen of the Hong Kong variant is so markedly different from 1957 strains it has been suggested that either the Hong Kong variant should have been called A<sub>3</sub> or we should revise criteria for classification. Assuming the animal data on the role of neuraminidase antibody applies to man and that neuraminidase antibody persists for one to two years (questions that are being investigated) then a reasonable prediction for the 1968-69 influenza season would have been that influenza would not achieve a worldwide pandemic state similar to that seen in 1957 and that pure influenza virus pneumonia, as distinguished from secondary bacterial pneumonia, would not be as common as in 1957. It is now a fact that the Hong Kong variant did not achieve the pandemic proportions of 1957. In addition, although the infection reached major epidemic proportions in the United States, surveys of medical centers indicated that cases of pure influenza virus pneumonia were uncommon.

It is essential to confirm the suggested role for neuraminidase antibody in man, and such studies are in progress in our laboratory and in others. Immunization of school children, the principal source of spread, with a purified form of the neuraminidase and hemagglutinin antigens, and immunization of all other persons with neuraminidase antigen only, might prevent epidemic influenza by reducing spread of infection. Additionally, widespread occurrence of hemagglutinin antibody, the presumed major stimulus for emergence of new variants, would not occur in this method of control.

Production of antibody to the hemagglutinin antigen of influenza virus by means of conventional vaccination continues to be the major approach to control. Development of serum antibody following parenteral vaccination with inactivated virus has been used for assessing vaccine efficacy since Francis conducted the first successful field trial in 1943. In the early 1940s Francis reasoned that the virus initially was deposited on the respiratory mucosa and that, to prevent initiation of infection, antibody must be present in respiratory secretions. He proceeded to demonstrate that antibody was present in secretions but believed it was derived from serum and that parenteral vaccination did an adequate job of providing secretion antibody. Studies by Fazekas de St. Groth in the early 1950s provided definitive information in animals that protection against influenza was better associated with antibody in respiratory secretions than in serum, but he too believed it was derived from serum.

Current knowledge indicates that a separate immune system is involved in production of secretion antibody. The major portion of such antibody is immunoglobulin A which sediments in the 11S region in the ultracentrifuge. It consists of two 7S IgA molecules connected by "secretory piece" and is commonly referred to as secretory antibody. It is synthesized in the submucosa plasma cells of the respiratory and gastrointestinal tract and perhaps other mucous surfaces as well. In an attempt to use this system to maximum advantage investigators have administered conventional inactivated vaccine topically\* in an attempt to provide more local antibody and greater protection. The most systematic evaluation of the antibody response has been provided by Kasel, who demonstrated that topical administration of vaccine was the only effective way to achieve high titers of secretory antibody in individuals with preexisting serum antibody. This probably accounts for the greater protective effect reported for aerosol vaccination as compared with parenteral vaccination in studies with strains prevalent before 1968. However, conventional parenteral vaccination produced equal or better antibody responses and protection than topical vaccination in all reported studies with the Hong Kong variant. This is probably because one or two topical applications is inadequate for persons with no previous exposure to the antigen. These combined results suggest that primary vaccination with a new variant of influenza should continue to be by conventional parenteral vaccination. Antigen administered in this way apparently reaches submucosal cells since a potent preparation administered in such a way will result in development of secretory antibody in a significant number of persons. However, the best method to revaccinate may be by means of a topical route.

The two major reasons why influenza vaccines did not receive wide acceptance in the past even in "high risk" groups were that available preparations were only marginally effective and they were too toxic. The introduction of more rigid controls of potency using standard reference vaccines is now in effect. A precisely measured 400 CCA unit dose has been shown to produce protection of 70 to 80 percent of subjects when given by conventional parenteral vaccination. Thus, marginally effective preparations should no longer appear for distribu-

\*Topically is used to refer to application of vaccine onto respiratory surfaces by means of nasal instillations and/or inhalation of aerosolized vaccine.



tion. In addition, new preparations are being made by methods that remove potentially toxic chick embryo proteins. Such preparations of influenza A are virtually nontoxic. However, despite new preparation methods influenza B vaccine has caused toxic reactions and the frequency of antibody response is low. Currently, only preparations containing both influenza A and B are available, but it seems reasonable to suggest that the monovalent influenza A preparations are so potent and nontoxic that they should be commercially available as such and that influenza B be withheld until a potent, nontoxic preparation is available.

An additional problem regarding vaccination has been availability of sufficient vaccine to induce protection in a susceptible population before a new variant arrives on the scene. The worldwide influenza surveillance centers are for this purpose and the Hong Kong center was the original source of the Hong Kong variant. Despite the fact that the elapsed time from original isolations of the Hong Kong variant to distribution of vaccine was considerably reduced as compared with what it was in 1957 for the original Asian variant, very little vaccine reached threatened areas in this country before influenza appeared.

Kilbourne recently prepared a recombinant (by a method called "strand exchange" in this symposium) of the Hong Kong variant and the laboratory-adapted PR 8 strain of influenza. This recombinant (called x-31) carries the hemagglutinin antigen of the Hong Kong variant and the growth advantage of PR 8. This latter strain grows to high titers in chick embryos, thus facilitating vaccine preparation. We found vaccine made from this recombinant to be equal to conventional monovalent inactivated influenza A<sub>2</sub>/Hong Kong in producing antibody and protection in man. Similar preparation of a recombinant, then, should facilitate the rapid preparation of large quantities of vaccine when influenza A<sub>3</sub> makes its appearance, an event that is certain to occur.

Comment should also be made concerning chemotherapy of influenza. Amantadine (Symmetrel®) has been clearly shown to prevent infection with influenza A. It prevents penetration of the cell by virus, a mechanism similar to that of antibody. I believe it should be recommended for unvaccinated "high risk" persons when exposed to influenza, and a recent report suggested optimal protection would occur in such persons

if they possessed some preexisting antibody to influenza virus. It may be that vaccine in the fall followed by amantadine on exposure to influenza in the winter will produce optimal protection. The possibility warrants trial.

Recently we tested the drug as a therapeutic agent. In a recent Hong Kong influenza epidemic, our results indicated increased rate of recovery from illness and a more rapid disappearance of virus from respiratory secretions in treated versus control patients. The effect was not dramatic but was nevertheless significant. The dose used was that recommended for prophylaxis, namely, 200 mg daily. No toxicity was observed with this dosage, and it was therefore felt that for treatment one could give a larger dose. Recently we gave 400 mg daily to three patients who were ill with pneumonia complicating influenza, and one of them, a pregnant woman, recovered in dramatic fashion. Controlled studies of the treatment of influenza pneumonia are not likely to be possible, and we may be required to pass judgment on the effect of amantadine on rather inadequate information. On the basis of our experience, we believe further such studies are indicated.

All in all, there is reason to be encouraged about the future. As stated by Dr. Stuart-Harris, despite a wealth of knowledge we are still defeated by the prowess of influenza virus. The occasion of this symposium is testimony to that fact. Nevertheless, a considerable effort is being made to defeat this redoubtable foe. In addition to the promising new developments cited in this editorial, there are many theoretical possibilities for improved control not yet examined. Among epidemiologists it is considered to be hazardous but essential to predict how serious the problem of influenza will be in any given year. To predict whether or not in the next few years optimal control of influenza will occur is certainly hazardous. Nevertheless, I shall predict that optimal control measures will be developed which will result in reduction of influenza to acceptable levels of occurrence, and that this will occur in considerably less time than has elapsed since the discovery of its cause.

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## Ferment in Medical Education

THE SPECIAL FORUM "Relevance for Today and Tomorrow in Medical Education," begun in January and concluded elsewhere in this issue, gives a glimpse into the ferment which is stirring in medical education. While the outcome is by no means clear it is certain that there will be change and much of it fundamental.

If one views medical education in the overall perspective of this century, he can grasp something of what has happened so far and perhaps a bit of what seems fairly certain to be in the offing. In 1900 scientific medicine was well started, but a practicing physician could still master most of the medical knowledge of the day and apply most of it himself in the care of his patients. At that time the Johns Hopkins faculty had just developed a concept of medical education which emphasized science and which was to set a pattern. The Flexner Report in 1910 accepted and ennobled this educational concept and it flourished thereafter. The strength of academia in medical education grew.

As medical science prospered and advanced so did specialization. No longer could any physician serve all purposes. Increasingly academia called the tune in both undergraduate and post-doctoral medical education and increasingly the tune became more and more research oriented. The benefits of this have been great. This very academically oriented system of medical education has brought about the most sophisticated levels of medical care to be found anywhere, a superb achievement. On the other hand it has failed to understand or to meet either the expectations or requirements of the society it tried to serve. The day of reckoning is now at hand and it is certain there will be new arrangements.

Right now the situation seems confused if not actually chaotic. One is reminded of the crysalis wherein the caterpillar undergoes transformation to a butterfly. Medical education is similarly undergoing fundamental change in form. There is departure from the past but the future has not yet taken shape. Yet significant forces are at work. Funds for medical research are being reduced substantially and by greater amounts than

many think is wise. The professions are determined that there be more student exposure to the various problems and types of practice and health care delivery. Society demands more and better medical services at less cost. Medical students have begun to influence their individual curricula in new and sometimes startling ways. The ferment is great, but there is little clear perception of where to go or what to do.

But as the remaining decades of this century are approached, some of the problems which lie ahead for medical education are becoming discernible. There will be more science and more knowledge to impart. There will be enormously greater numbers of people to be served, not only in this nation but throughout the world, if there is to be either health or peace on this planet. Problems in pollution will increase in parallel with population and essential industrialization. Understanding and protecting the ecology of "spaceship earth" will become of crucial importance to the health, well-being and survival of all mankind. The scope and responsibility of the physician's work will taken on new dimensions. New methods, new skills and new kinds of personnel will be needed and medical education itself will require new instruments and new techniques.

The forum on "Relevance for Today and Tomorrow in Medical Education" has provided a glimpse of what many think the future will bring. But it has not answered the essential questions: What will the physician be expected to know and to do, what will the true needs of society be, or to what should medical education be relevant during the next ten, twenty or thirty years? There is sure to be great waste of money, time and effort on the part of medical educators and a lot of other people until there is some greater consensus with respect to this. The parties at interest include the educators, the students, the consumers and their government, but they cannot solve this problem either alone or together without help, guidance and even leadership from the broad spectrum of the medical profession. It now becomes a public and professional responsibility for medicine to provide this help, guidance and leadership. This year, 1970, might even be a good time to launch another "Flexner Report" which would address itself to these questions. Whatever is to be done should be done soon. We should not forget that it is the medical student of today who will be in his prime of practice in 1980, 1990 and 2001.

## Capitation Health Care

THERE IS ABUNDANT evidence that planners in the federal government have decided that capitation health care will substantially reduce costs and they are promoting this form of financing the delivery of health care with all the substantial resources at their command. This began with the touting of closed panel prepaid group practice programs, of which there are several, successful and satisfactory, in the West. At the beginning, financial incentives were offered to physicians to establish such practices, and now it is proposed to use the powerful instrument of the federal Medicare program to further the cause.

So far as is known the decision process which arrived at this conclusion has never been revealed. It is well known to have been favored by persons in influential places who discuss the broad picture as they believe it to be, and then determine what ought to be done. It would appear that among these persons many have held the belief that capitation health care is considerably cheaper than fee-for-service, and it is presumed that this is because services can be rendered less expensively and because there are thought to be built-in incentives to render fewer rather than more patient care services.

There is a large and growing experience with capitation health care and there is no doubt that it has a rightful place in a pluralistic system of health care delivery. But it is also a notable fact that it has not swept the country as would be expected if it really satisfied all needs—and this in spite of considerable publicity and not a little federal support. Recently, and no doubt significantly, some responsible purchasers of capitation health care have begun to question the real extent of the economic savings with this system of care as it now exists and have started to look for alternatives.

The cost of health care is a serious national problem and it is safe to say that health care delivery will henceforth be increasingly money-oriented. But the individual services and even

the delivery system itself must also be oriented to the patient and to the doctor if the human needs are to be met. Perhaps what is needed is more experimentation with imaginative new ideas rather than an intensive promotion (with government funds) of a system which may or may not in reality be much cheaper and which certainly has sold itself less than completely even after more than 25 years of promotion and demonstration. There will be no difficulty in finding ready acceptance for any programs which are really much better or much cheaper. They will fly by themselves without any special federal inducements, carrot or stick.

## The Galloping Ghost of Gauss And the "Normal" Radioiodine Uptake

THERE IS, AMONG the young, a popular refrain that says "the times, they are a-changin'." And there is truth in the statement. Therefore, no one should be surprised when the usually accepted values for a well known laboratory procedure seem to be abruptly altered. Rather we should be grateful that our intellectual somnolence is disturbed, enabling us to avoid translating information into misinformation to some patient's detriment.

Recently two studies with regard to the radioiodine uptake by the normal thyroid gland have been reported<sup>1,2,3</sup> from widely separated parts of the United States. Both the study from Birmingham, Alabama, and the study from north-central California indicate that within the past decade there has been a dramatic decrease in the values observed in the 24-hour radioiodine uptake obtained from patients who are clinically normal. Pittman<sup>1</sup> suggested that expansion of the iodide pool from dietary sources may explain this apparent decrease.

For the past several years the phenomenon of lowered normal values has been empirically noted



in the laboratory in my office. No precise data was obtained as only patients suspected of thyroidal abnormalities were examined. Keating<sup>4</sup> and his associates argued well that valid data regarding normality cannot be extracted from a mixed population of diseased patients and supposed normals. To establish the range of expected clinical variation a population of healthy patients must be tested.

The change to lower normal values immediately poses two questions. Are there patients with true hyperthyroidism whose present 24-hour uptake studies are normal by the older criteria of normality (15 percent to 45 percent) but are clearly abnormal by the more recent studies? And has the "normal" curve been so displaced to the left that the radioiodine uptake study, which is a weak enough tool in helping to diagnose hypothyroidism, becomes virtually worthless?

In the attempt to answer these questions we must first address ourselves to the problem of statistical normality. How can we establish the usual limits of clinical variation in patients we believe to be normal. For the radioiodine uptake study at 6 hours and at 24 hours, what is the normal range?

No sophisticated scientist today would rise before an erudite audience and say, "I believe in ghosts." Nevertheless the ghost of Gauss rides roughshod through our scientific literature, enticing us to make unwarranted assumptions and permitting unwise bias to enter our differential diagnostic thinking. The seductive symmetry of the normal, bellshaped Gaussian curve can lead us down the scientific primrose path.

Most physicians have at least a nodding acquaintance with the mean, median and mode, but a discussion of the relative effectiveness of these measures of central tendencies to any specific problem is best left to professional statisticians.

If our biologic data really do approximate a true normal curve, then the mean, plus or minus two standard deviations, may well define the clinically normal range. Sadly, such is not the case in most biologic studies. The frequency distribution curve may be seriously skewed (usually to the right) or too peaked or too flat to allow application of the simple formula  $X \pm 2\sigma =$  the normal range.

In 1960, seduced by the ghost of Gauss, the normal value for the 24-hour uptake in my office laboratory was determined to be a mean of 26

percent  $\pm$  7 percent as the standard deviation. Our normal range then was 12 percent to 40 percent. These figures were a little lower than the widely quoted 15 percent to 45 percent. Pittman reported,<sup>3</sup> in the Birmingham study, a mean of 28.6 percent  $\pm$  6.5 percent as the standard deviation in 1959. These figures are quite similar to ours, but approximate the 15 percent to 45 percent range more closely.

Currently the figures from the Birmingham study show a 24-hour mean of 15.4 percent with a standard deviation of 6.8 percent. By the Gaussian interpretation the normal range would lie between 1 or 2 percent and 29 percent, virtually eliminating any possibility of suspecting hypothyroidism because of low values.

Bernard<sup>2</sup> reported from north-central California a 24-hour mean of 15.57 percent with a standard deviation of 4.49 percent. The range of normal then would be 7 percent to 25 percent.

By plotting the frequency distribution of our data obtained from 103 healthy persons (85 women aged 18 to 69 years and 18 men 19 to 56 years) on the usual  $x, y$  coordinates and on probability paper, a clearly non-Gaussian curve, skewed to the right, was obtained. For the sake of comparison the mean and standard deviation was calculated for both the 6-hour study and the 24-hour study (See Table 1). Our 24-hour mean is 18.7 percent and our standard deviation is 5.9 percent. The fallacious Gaussian normal range would then be 7 percent to 30 percent.

Keating<sup>4</sup> suggested that where the shape of the actual curve does not approximate the normal frequency distribution, ranking the data by percentile may be a more reliable method of determining the usual range of clinical variation. By including as normal the group lying between the 2.5 percentage point and the 97.5 percentage point, 95 percent of our healthy population have a 24-hour radioiodine uptake between 10 percent and 30 percent. These figures are in excellent agreement with the range of normal used at the National Institutes of Health.<sup>5</sup> The 6-hour range in my office laboratory lies between 4 percent and 18 percent.

TABLE 1.—24-Hour Radioiodine Uptake

	1959-60	1969
Birmingham <sup>1,3</sup>	28.6% $\pm$ 6.5%	15.4% $\pm$ 6.8%
North-central California <sup>2</sup>	.....	15.57% $\pm$ 4.49%
San Diego <sup>4</sup>	26.0% $\pm$ 7.0%	18.7% $\pm$ 5.9%



If 10 percent is used as the lower limit of normal, there remains room for abnormally low results to make the physician suspect hypothyroidism. At the upper end of the scale we have seen and may expect to continue to see patients suffering from true hyperthyroidism with 24-hour values lying between 30 percent and 45 percent.

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## THE VALUE OF CULTURES IN SORE THROAT

"The great advantage of a throat culture in the child with a sore throat is that it points up the epidemiology of the community situation, especially by season. If it's summer and you see a sore throat that's exudative and get a couple of negative cultures in succession, you can be quite sure you're dealing with a nonstreptococcal enterovirus or one of the unidentified causes of nonstreptococcal exudative pharyngitis. All you need in the summer is a few negative cultures to give you confidence that the community is having a little epidemic of viral pharyngitis due to an exudate-producing strain.

"Similarly, if it's late fall and you get several positive cultures in a row of Group A streptococcus, even a red throat is going to be highly suspect.

"If you don't have throat culture facilities immediately available, you can send them in to the state health laboratory. If you send a few cultures in and they come back positive, you get a very strong impression of what you're dealing with in the community at that time. So a few cultures will give you a huge educated guess. . . . I can't see any great excuse for not knowing the epidemiology of the sore throat you're handling."

—GENE H. STOLLERMAN, M.D., Memphis  
Extracted from *Audio-Digest Internal Medicine*, Vol. 16, No. 4, in the Audio-Digest Foundation's subscription series of tape-recorded programs.

# LETTERS to the Editor

## On Quick Test Uses

*To the Editor:* It is gratifying to note that Perkins and Biben in their paper (Calif Med 112:1-7, Mar 1970) on long-term anticoagulants felt justified to comment: "The results indicate no benefit from supplementation of the Quick tests by any of these other procedures. It suggested that the Quick test uniformly performed, using a standard thromboplastin, would be the procedure of choice." It is difficult to understand, however, one of their statements: "The data obtained with the study indicate that, for all of its defects, the Quick prothrombin time method remains a satisfactory technique for control of anticoagulant therapy . . ."

It should be greatly appreciated if the authors would enlighten me as to what these defects could be. To be sure, the one-stage method is not a specific, quantitative measure of prothrombin, except in uncomplicated hypoprothrombinemia. In oral anticoagulant therapy the one-stage test is mainly a measure of Factor VII depletion, provided a thromboplastin reagent is employed which is devoid of Factor VII as an impurity. The reagent, acetone-dehydrated rabbit brain, which I developed in 1938, is probably the most trustworthy reagent available for coagulation studies. It is not only free of all components of the prothrombin complex but it has remarkably high and uniform activity and great stability. Material prepared and sealed in vacuum in 1938 still gives a 12 second prothrombin time with normal human plasma. Because of its great sensitivity to lack of Factor VII, it has proved to be the only satisfactory means to measure Factor VII in plasma, which, although it is not required for intrinsic clotting, is needed in hemostasis and its deficiency may result in severe bleeding. Even though the vogue of anticoagulant therapy may pass, the one-stage prothrombin time and its companion test, the prothrombin consump-

tion time, are likely to remain as key tests in the diagnosis of coagulation defects. Acetone-dehydrated rabbit brain will probably endure as the reagent of choice.

The prothrombin consumption test is equally as basic a qualitative coagulation test as the one-stage prothrombin time. It seems puzzling, therefore, that in the Medical Staff Conference on Differential Diagnosis of Platelet Dysfunction (*ibid.*, pg. 66), no mention was made of this test for the detection and the diagnosis of thrombopathy. Just as the prothrombin time is sensitive and definitive for the vitamin K-dependent prothrombin complex factors, so is the prothrombin consumption test sensitive to Factors VIII and IX and to the platelet clotting factor.

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## The Authors Reply

*To the Editor:* I am in full agreement with the statements in Dr. Quick's letter and am happy to have occasion to pay tribute to the importance of his pioneer observations. Our comment regarding the defects of the Quick prothrombin time method was directed at the points outlined in his letter. The test is a useful and most necessary technique for detecting deficiencies of factors II, V, VII, X and fibrinogen. It is more sensitive to deficiencies of some of these factors than others. In terms of its use in monitoring patients on oral anticoagulant therapy, it almost entirely reflects changes in factor VII in the first day or two; with long-term therapy, the correlation between Quick prothrombin times and individual clotting factor levels is somewhat different, as outlined in our paper. The Quick test is affected by factor V (which is not depressed by oral anticoagulant therapy) but

not by factor IX (which is). I think it fair to call these "defects" of the test in terms of monitoring the patient on oral anticoagulant therapy, but I conclude, with Dr. Quick, that it is the procedure of choice.

I am also in agreement with Dr. Quick as to the usefulness of the prothrombin consumption test to detect platelet dysfunction, although I prefer a modification of his technique for this purpose.

We do a specific assay for factor II (prothrombin) in plasma and serum. Abnormal consumption of prothrombin is confirmed to be caused by a platelet defect when normal results are obtained in a duplicate tube in which blood has clotted in the presence of an optimal amount of cephalin, a platelet substitute.

Dr. Sahud's discussion of platelet function tests concerned newer knowledge about platelet plug formation and did not discuss in any detail the other role of platelets in hemostasis, the provision of phospholipid (platelet factor 3) for coagulation. Dr. Sahud did point out that platelet factor 3 availability could be impaired in qualitative platelet defects. Dr. Quick is quite correct in pointing out that a test for platelet factor 3 is a necessary part of a study of qualitative platelet activity.

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*To the Editor:* Dr. Quick states that the prothrombin consumption test is sensitive for the detection of the platelet clotting factor. We have performed the prothrombin consumption test on all cases of platelet dysfunction. In the three cases of macrothrombopathia we have studied, the prothrombin consumption test was abnormal as well as other tests of platelet factor 3 availability. However, in five of seven patients with normal size platelets who have a primary platelet disorder as previously described,<sup>1</sup> prothrombin consumption (as measured by a standard method<sup>2</sup>) was normal whereas platelet factor 3 availability by the kaolin method<sup>3</sup> was clearly abnormal.

It may be that the prothrombin consumption test measures a different aspect of platelet procoagulant activity than the kaolin method. In any

event, the prothrombin consumption test in the platelet disorders with defective collagen-induced aggregation and normal platelet size has been less sensitive in our hands.

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## Fads, Facts, Fundamentals

*To the Editor:* Whoever wrote the editorial about "Costly Myths in Medicine" [*Calif Med* 112:81-82, Mar 1970], said exactly what I have felt needed to be said for a long, long time. Let's have more of the same instead of the completely unopposed and discussed idiotic ideas of current fads and fancies with a complete neglect of facts and fundamentals.

How about a column where some of us could write in and point out some of these things once in awhile?

CHRISTOPHER A. MASON, M.D.

*Los Angeles*

How about *this* column?—EDITOR

## Amniocentesis Registry

*To the Editor:* Recently there have been two editorials, one in the March 12 issue of *New England Journal of Medicine* by Dr. John Littlefield, and the other in the February issue of *Archives of Environmental Health* by Dr. Robert Cooke, as well as a Medical Progress article in the February issue of *CALIFORNIA MEDICINE* on recent advances in intrauterine diagnosis for chromosomal and metabolic disorders. There are a large number of such inborn errors of metabolism which can be diagnosed by amniocentesis. Each requires



special procedures and techniques, so that no single center can be expected to be fully proficient to perform all possible tests. The first two gentlemen pointed out the need for establishing a directory or registry of centers identified with the procedure or disorders they are competent to undertake. We have had the same concern and indeed decided to establish a registry of amniocentesis capabilities in the Western States. A survey was conducted of Centers and investigators wishing to participate in a collaborative effort to pool amniocentesis resources were invited to submit a list of the capabilities of their group. An essentially unedited compilation was made. The "Western States Amniocentesis Registry" which evolved contains a listing by Center and investigator iden-

tified with cytogenetic or biochemical capabilities and contact addresses and telephone numbers. At this writing, the Registry has just been completed and is being distributed to the participants. Since additional procedures are being tested and new capabilities will be acquired, an updated master file will be maintained at Pacific State Hospital.

We believe that it would be propitious to make an announcement in your organ that such a list now exists and suggest that those who may have occasion to avail themselves of the services should contact this laboratory.

HAYATO KIHARA, PH.D.  
*Chief Research Biochemist  
Pacific State Hospital  
Pomona, Ca 91766*

### "PSYCHIC ANESTHESIA" IN OBSTETRICS

As an anesthetist, what do you do when the obstetrician tells you to put a woman to sleep who has just eaten a half hour ago?

"Don't stop to argue. When you run into a delivery room and the patient is crowning, you don't ask questions. You don't have time to do an epidural; you haven't got time for a caudal; you haven't got time for a spinal. . . . There is a very good way to handle this. . . . You dash in, grab the mask, clap it on her face, turn on the oxygen, and say, 'Lady, take deep breaths; it will ease the pain.' She does take deep breaths of oxygen; the pain goes away; the baby comes out; everybody is happy; and all she has gotten is oxygen.

"The importance of suggestion in this situation is very great, indeed. The patient doesn't need an analgesic because what we're doing is conducting instant hypnosis. You put the mask on her face; a cold freeze blows on her; you say, 'Take deep breaths'; you get the hyperventilation phenomenon plus the suggestion; and the patient almost invariably says, 'Doctor, I don't know what I would have done if you hadn't come along with that mask to help me out.' I think this really solves a very important problem."

—JAY J. JACOBY, M.D., Philadelphia

Extracted from *Audio-Digest Obstetrics and Gynecology*, Vol. 16, No. 5, in the Audio-Digest Foundation's subscription series of tape-recorded programs.

## *Information*

### Tetralogy of Fallot

JAMES R. MALM, M.D.

*Material Supplied by the American Heart Association*

**TETRALOGY OF FALLOT** is a totally correctible cardiac anomaly accounting for 30 percent of all cyanotic heart disease in infants and previously associated with a 25 percent mortality in the first year of life. While the original anatomic description of this defect included dextroposition of the aorta and right ventricular hypertrophy, these phenomena are secondary to the basic abnormalities, namely a large ventricular septal defect and severe outflow tract obstruction from the right ventricle. The hemodynamic result is shunting of systemic venous blood across the septal defect to the left ventricle resulting in peripheral cyanosis and reduced pulmonary blood flow. The degree of outflow obstruction is dynamic, varying with the infant's level of activity or excitement; thus the level of cyanosis may change decidedly from moment to moment.

Cyanosis in an infant is an indication for complete diagnostic studies including cardiac catheterization and angiography. Catheterization at this age is safe and by the results one may establish an anatomic diagnosis, providing clear guides for future management. Life-threatening syncopal episodes, secondary to cerebral hypoxia, or other signs of severe reduction in pulmonary blood flow are an indication for a palliative systemic to pulmonary artery shunt. The recent use of anastomosis of the right pulmonary artery to ascending aorta has provided excellent increase in pulmonary blood flow, although the procedure is associated with a significant mortality in infants below six

months of age. Cyanosis, exertional dyspnea and squatting may not appear until the child's demands for oxygen increase as he begins to walk. A shunting procedure is recommended for symptomatic toddlers and children under four years of age to relieve symptoms, to permit normal growth and development until the patient reaches the age at which total correction can be carried out with a low mortality. We recommend carrying out total correction on any symptomatic child over the age of four years, whether or not a shunting operation was done previously. Elective total correction of the anomaly is indicated in the relatively asymptomatic child between the ages of seven and ten years. The effectiveness of the palliative shunts decreases in 60 percent of patients as the oxygen demands increase with age, and endocarditis develops at the site of the surgically created ductus in 7 percent of cases. All patients with functioning shunts should be reevaluated for total correction before age 15.

Total correction of this anomaly requires closure of the ventricular septal defect, relief of the outflow tract obstruction of the right ventricle, and ligation of any existing previously constructed shunt. The correction can be carried out with a mortality of less than 10 percent and the postoperative course is directly affected by the completeness of the surgical repair. When a complete repair has been carried out the postoperative course is benign, without evidence of cardiac failure or pulmonary complications. Correction is sometimes limited by the presence of multiple small septal defects or an extreme degree of narrowing, even hypoplasia, of the outflow tract of the right ventricle. When the outflow tract is decidedly narrowed, an outflow tract patch or gusset is required to increase the size of the pulmonary annulus. This patch results in pulmonary valvular insufficiency and is usually associated with moderate to severe degrees of right heart failure during the first two to three weeks after operation. Digitalization is required for two to three months, but no cardiac limitations have been noted in long-term follow-up. An extreme form of the anomaly is complete absence of the pulmonary artery. Defects of this type can now be repaired by using a preserved human aortic homograft as a conduit between the right ventricular outflow tract and the main pulmonary artery. This provides a graft with aortic valves functioning at the pulmonary valve level, avoiding a pro-

The author is Professor of Clinical Surgery, Columbia University, The Atchley Pavilion, New York City.

nounced degree of pulmonary valvular insufficiency. These grafts have improved the immediate postoperative management of these patients.

The late postoperative results have been dramatic. After correction of the defect, patients have normal exercise tolerance and no evidence of cyanosis. In our own series postoperative catheterization data suggests that over 90 percent of

the patients have normal or nearly normal postoperative hemodynamics. In addition, late hemodynamic studies with exercise demonstrate that these patients have a normal response in cardiac output to exercise. We feel that these postoperative studies and the maintenance of excellent hemodynamics in a follow-up period suggest that longterm outlook is excellent for these patients.

### PREPARING THE CHILD FOR SURGICAL OPERATION

"In our intensive care areas, there are more and more monitors, various types of oscilloscopes, and instruments used for recording various physiologic reactions to surgery. I would like to mention that two twin oscilloscopes have a decided resemblance to many of the robot monsters on television. I have had more than one child say that the machine's 'eye' was looking down to find out exactly what he was doing while he was in the intensive care area. I think these represent considerable threats, not only to children but to parents.

"Our policy is to show the child one of these monitors, give him a chance to look at it, touch it, talk to it if he wishes, and feel his way around before he has his surgery. . . . Parenthetically, we also bring the parents into this environment before the surgery, if we possibly can, so that they will not be concerned about the various instruments.

"Another concern of children is the oxygen tent. This is particularly applicable to the cardiovascular and thoracic patient. An opportunity to climb into a tent beforehand and to get his mother to put her head in can be a very satisfying experience for the child in terms of realizing that it does not constitute a threat. The last time he heard about an oxygen tent was when his grandmother in congestive heart failure died in one. Therefore it's of considerable consequence to see that this can be just one of the playthings present in the intensive care area."

—J. ALEX HELLER, JR., M.D., Baltimore

Extracted from *Audio-Digest Surgery*, Vol. 16, No. 3, in the Audio-Digest Foundation's subscription series of tape-recorded programs.



## CMA and the Seventies

ALBERT G. MILLER, M.D., *San Mateo*

TEN YEARS FROM TODAY—at the start of the next decade—it is probable that one of you now seated here as a delegate or alternate will be standing in my shoes. Then, having spent two years in the highest offices the California Medical Association can bestow, you will try to find words to tell your colleagues what your “stewardship” years have taught you and where medicine stands at the close of the 1970s. I cannot predict what your story will be, but I can predict that it will be an exciting story of unprecedented change in nearly all facets of health care delivery as we know it.

Right now some of you may be asking yourselves, “But wasn’t change the keynote of the sixties?” To you, I submit that “We ain’t seen nothin’ yet!”

And I believe that each of your presidents who stood in the line of fire during the sixties would agree with this statement. If we can characterize the sixties as traumatic, the seventies will surely be tumultuous. The seeds of change have been sown and have taken root—in tremendously fertile soil. The climate of public opinion speaks loudly for itself—in the newspapers, in the halls of Congress, on the campus, in the streets and in the courtroom.

What can we learn from our experiences during the sixties to help us play an effective role in the explosive decade ahead?

1961. A “first” for California—the Guiding Principles for Physician-Hospital Relationships and Medical Staff Survey Program are launched. Kildare and Casey are joined on TV by the “Doctors at Work” series. The House of Delegates approves

a merger of the medical and osteopathic professions by a vote of 296-3. California becomes the first state to undertake a formal accreditation program to elevate standards of care in nursing homes. This House approves the creation of the California Medical Education and Research Foundation—another CMA “first.” President Warren Bostick goes to Washington to present CMA testimony at Congressional hearings on King-Anderson. He speaks strongly in favor of Kerr-Mills.

1962. Kerr-Mills is implemented in California and CMA goes all out in support. “K. O. Polio” campaigns blanket the state. President Bill Wheeler presents a charter to the Forty First Medical Society—contingent on passage of Proposition 22. In November, Proposition 22 wins public support by a “2 to 1” margin.

1963. CMA’s Scientific Board is established “to bring the profession together.” We become the first medical association officially to damn cigarette smoking as a health hazard. CMERF earns national support for its studies. With our urging, a “blue ribbon” commission to overhaul the Workmen’s Compensation system is established. At the request of the state, CMA surveys mental facilities. Reaffirmation of decentralization of care for the mentally ill. King-Anderson again. The first “Role of Medicine in Society” study is published. CMA urges the Legislature to broaden Kerr-Mills and ease its eligibility requirements.

1964. President Sam Sherman is congratulated by Wilbur Mills for his excellent testimony before Congress on the King-Anderson Bill. California Blue Shield celebrates its 25th anniversary with more than a million members.

1965. On closed circuit TV, Jim Doyle unveils CMA’s new health care plan for the aged—main-

Dr. Miller’s presidential address was presented before the House of Delegates of the California Medical Association, March 7, 1970.

Reprint requests to: California Medical Association, 693 Sutter Street, San Francisco 94102 (Dr. Albert G. Miller).

stream care, without the stigma of charity for medically needy persons over 65. AMA pushes "Elder-care." CMA establishes a clearing house to avoid duplication of postgraduate education opportunities for physicians. Ralph Teall goes to Washington to testify on a new omnibus federal proposal containing features of King-Anderson—it is dubbed "Medicare." Governor Brown signs six CMA-supported legislative bills designed to broaden the disciplinary powers of the Board of Medical Examiners.

And then that wonderful year, 1966 — Medicare becomes law. And in spite of our long campaign in opposition to any approach which disregards need, CMA now offers to governmental agencies and others the cooperation of physicians in guiding implementation of the law. The much-altered CMA-sponsored Medi-Cal program also becomes law—a state measure by now amended to implement Title XIX. Testimony by CMA brings major improvements in the state Workmen's Compensation program: enlargement of the panel of physicians, creation of a medical advisory committee, and a new minimum fee schedule, utilizing the 1964 edition of the *RVS*. Jim MacLaggan warns California physicians that they are in a goldfish bowl, with other states watching how the principle of reimbursement based on reasonable charges works under government programs. Quoting Bob Dylan, Ralph Teall exorts us to awaken to the fact that "The times, they are a-changin'."

1967. The first Medi-Cal fiscal crisis. Jack Morrison pledges CMA's cooperation in continuing to provide the best care possible under the emergency cuts, but strongly urges restoration of the basic components of AB 5. CMA again is asked to survey the state's mental facilities. Our first joint Congressional Visitation with Blue Shield. First conference with representatives of medical specialty societies. Legislative efforts to alleviate professional liability problems.

1968. Professional liability problems mushroom. A breakthrough of sorts with passage of three CMA malpractice bills. Intensive study into the doctrine of *res ipsa loquitur*. Malpractice prevention workshops conducted throughout the state. Development of refined guidelines for utilization review committees. The State Attorney General's report on Medi-Cal and President Todd's immediate response. A package of legislative recom-

mendations aimed toward improving the Medi-Cal program. Passage of the Professional Corporation and Lanterman-Petris-Short Acts. CMA statement on the ethical and legal implications of transplants.

1969. Professional liability problems grow to crisis proportions. Again, CMA manages to push through three new laws to alleviate the situation and approves a strong professional liability legislative platform for 1970. We join with hospitals to initiate a pilot project in arbitration. Employment of an independent actuary of national reputation to conduct a thorough investigation of the problem (you have received his report). In response to House action on continuing education, development of the specific administrative mechanisms to enable CMA to collect, code and certify physician participation in accredited postgraduate education. Gearing for statewide surveys of long-term care facilities. The first "Guiding Principles." Major contributions by CMA to prevent Medi-Cal abuses through legislation and stepped up peer review activities. Involvement of medical students in CMA committee activities.

That doesn't sound like a docile, do-nothing, status-quo organization to me! We have proposed more than we have opposed; we have initiated more than we have vacillated.

### Anticipating Problems and Needs

We can all take pride in CMA's record during the sixties, but I believe it has taught us at least one lesson. When we succeed, it is because we have recognized problems and seized the initiative; when we fail, it is because recognition came too late and our response was too little. Anticipating problems has never been easy; during the current crisis of change, it will require an almost superhuman effort. In the seventies, our basic problems will not merely persist, they will multiply, growing at a rate which staggers the imagination. Not because we belong to the medical profession, but because we are part and parcel of a socio-economic revolution (not evolution!) that is rocking America even as we sit here today.

What are some of the facts underlying this revolution? Our rate of population growth: by 1985, there will be over 64 million more Americans to be fed, clothed, housed, educated and cared for medically. That amounts to as many more people



by 1985 as now live in all 24 states west of the Mississippi River. It means 165 patients tomorrow for every 100 we have today.

Young people will make up the greatest part of the U.S. growth during the next two decades. In just a few years, half of our population will be under age 26.

In the next seven years, health expenditures are expected to double. This will be the result of a spiraling demand, caused not only by population increase, but by rising personal incomes, higher educational levels, urbanization, our own improved medical capabilities and broader prepaid health care programs—both government and private.

Within two years, health will be the nation's No. 1 industry. If we think the politicians are preoccupied with criticism of our health care system now, wait till we're No. 1! Even the traditionally moderate U.S. Chamber of Commerce points toward greater government involvement as the only logical answer to the mammoth problems concerning the health and well-being of a growing number of Americans. Even now, government is paying for nearly 40 percent of the total health care package.

## Medicine's Role in the 1970s

What role will medicine play during the 1970s? The role of *critics*, content to point out weaknesses in solutions posed by others? Of *scholars*, choosing to study problems throughout the decade until we think we have an infallible solution? *Will we ignore the existence of problems* until it is too late for us to participate in the formulation of any solution? Or *will we profit from the lessons of the sixties*?

Let's take a look at just three of the central issues in this revolution: *manpower, standards, and financing* of care.

To meet our nation's health manpower demands, we now need over 50,000 more health personnel than we have; in five years that figure will have risen to 100,000. We are aware that the health manpower problem means much more than just total numbers of persons. In 1910 there were 40 allied health professionals for every 100 physicians; today there are 1,400 allied professionals for every 100 physicians. Two major approaches to the health manpower problem are now being vigorously pursued: (1) increasing

the numbers of health professionals, and (2) creating new categories of auxiliary health personnel. We physicians have long encouraged the growth of the "health team" concept. It is a large and diverse team with all degrees of skill required: the nurse, the technologist, the technician, the therapist, the podiatrist, the pharmacist, the computer analyst, the engineer, the ambulance driver, the hospital orderly, the bookkeeper, the record room librarian, the ecologist—all contribute to the care of the patient. But as these types of personnel proliferate and others are added—at a necessarily astounding rate—will the result be better patient care? Will this be coordinated effort to place the right number of the right kind of qualified health personnel in the right place at the right time? Or will it be chaos in which quality is smothered and delivery is fragmented? And who will prevent this chaos? Who is capable and willing to lead in the complex task of delineating the need as well as the precise duties, education, certification and extent of liability for both the newer and the traditional helpers?

I believe that this is a job we cannot abdicate or delegate. Neither can we do the job alone. We must involve the many other disciplines who will be so profoundly affected—educators, hospital administrators, licensing agencies, legislators, government officials and, of course, the allied health professions themselves. If we do not immediately rise to the challenging task of becoming "prime coordinator" in this essential area, then I think we are failing not only our patients but ourselves.

I believe it is in the interests of our patients that we remain captain of the health care team—a position that carries with it more responsibilities than honors.

## Quality First

Another tremendous challenge to the medical profession—assuring our "patient-public" of high quality medical care. We have long carried the banner for "quality"—this has, in fact, been the single most important factor underlying our positions on almost any health issue I could mention. In the final analysis every CMA activity is geared to the profession's prime commitment: quality patient care.

From the Flexner Report in 1910 to the now emerging programs for certifying physician participation in continuing medical education, we



have been the leader. Why, then, the current public concern over quality?

Again, the causes can be traced to the changing social environment of which we are a part. The knowledge explosion: we have discovered more scientific facts in the last 30 years than we have in all the rest of time. We will discover more scientific facts in the next five years than we have in the last 500. Add another component—the growing demand for “quality” in all facets of life by an increasingly well educated and affluent society. The consumers of medical care during the seventies will not just ask for reassurances of quality; they will demand guarantees.

Are we prepared to give such guarantees? Or will we be lost in the shuffle—as others, who may be well-intentioned but certainly less qualified, rush to establish and enforce standards for us and upon us?

Medicine has laid the foundation for demonstrating the competency of physicians. We have been instrumental in upgrading standards for medical schools. Since 1934, CMA has sponsored its own postgraduate education programs to keep physicians up to date, and this year we will be taking a giant step by approving a formal certification program to acknowledge their accomplishments. CMA certification, incidentally, is not an impromptu response to current public pressure. This idea was advocated at the first “Planning and Goals” conference in 1967 as an expression of continuing concern with quality.

Through innovative *peer review* activities, we have brought to life our conviction that quality medical care rests on a foundation of professional self-evaluation. Our medical staff survey program has become a prototype for the nation; the long-term care survey program holds the same promise.

Yet there is much to be done. There are many powerful segments of the public who are far from convinced. You are aware of current legislative proposals which call for a periodic reexamination for medical licensure. I think I can speak for you in stating that a society which measures the excellence of its healers by their ability to cram for a sterile examination every four years, may deserve what it gets. At least a dozen other cogent disadvantages to this kind of system can be pointed out.

But again, the *real* question is whether our own answer is persuasive enough to offset the rash or destructive solutions which are being offered. On

this issue we have seized the initiative. Our challenge now is to retain it through broadening, refining, integrating and publicizing our approaches to continuing education and peer review.

### New Methods of Financing Care

And now we come to the most crucial issue facing us in this decade—new methods of financing medical care to assure its accessibility to all citizens. CMA’s concern with the availability of health care to all is as old as our organization. Concrete evidence of our concern dramatically appeared in 1939 when CMA subsidized the early operation of a new approach in the insurance field—prepaid medical care. The idea behind the establishment of California Physicians’ Service was startling in 1939. Today, some 80 percent of the nation’s population have some form of voluntary medical insurance.

A few minutes ago our “instant replay” of the sixties told another essential part of the story—medicine’s continuing commitment to improving government health care programs for the needy. Today a large part of our energies go toward attempting to improve the Medi-Cal program, just as in the last decade we continually sought improvements in the original Kerr-Mills approach.

In the volatile seventies, a new national approach is advocated as the only answer to the increasing demand for medical services. You are aware of the mounting public pressure for some form of universal health coverage. Today, it’s virtually impossible to find any publicly stated lay opposition to the concept.

President Nixon, for example, who flatly opposed such a program during his 1968 campaign, said last July, “The nation’s health care problems were much greater than I had realized . . . a massive health-care crisis affecting millions of people is in the making.” These words were followed by action—a directive to Secretary Finch to investigate the feasibility of a National Health Insurance Program. HEW’s Medicaid Task Force was asked to study the issue. Meanwhile, the nation’s governors—three-fifths of whom are Republicans—voiced their support for a national health insurance program. The president of the American Hospital Association recently predicted compulsory universal health insurance within five years.

The list goes on and on, and I haven’t yet mentioned Walter Reuther’s plan or Representative

Griffith's AFL-CIO proposal. The question no longer is *whether* this concept will be implemented. It is *how* this concept will be implemented.

### Our Role in the Changes to Come

Faced with the certainty of revolutionary changes in financing of health care in this decade, what is medicine's role? The answer is obvious. We must assume the initiative in developing and promoting the kind of voluntary universal health benefits which will advance—rather than retard—quality health care for all. We must aggressively pursue the enactment of a program which embodies these essential elements: (1) free choice of physician and hospital; (2) “mainstream” medical care; (3) free choice of approved programs of coverage; (4) degree of financial assistance based on need; (5) full use of existing voluntary health insurance mechanisms. In other words, we must defend and support not a “locked in” bureaucratic single approach, but a pluralistic approach to meet the pluralistic needs of society.

Through public and professional media, you have been made aware of the ingredients of currently prominent national health insurance proposals, of which there are now nearly a dozen. Their price tags run from 11 to some 40 billion dollars. Four of them are compulsory and three would radically change the whole delivery system. Three involve no participation of voluntary insuring mechanisms and call for a federal agency to be the sole administrator, with no responsibility delegated to state government.

AMA has introduced its “Medicredit” proposal, which does embody the essential elements mentioned a moment ago. But this is only a beginning. Through the CMA delegation to the AMA, your CMA Council expressed its deep concern late last year that organized medicine must intensify its efforts to develop realistic and effective plans of voluntary universal health care coverage. The AMA House accepted the intent of CMA's resolution and has urged CMA and other state medical associations to submit promptly other realistic proposals. We already have begun work on this assignment; our preliminary ideas are outlined for you in the supplemental report of the Council to the House. We believe that all the resources Medicine can muster—and more—must be brought to bear on this crucial issue. The stakes have never been higher—our actions can be no less.

The urgency inherent in the problems of this decade were brought even more forcefully home to me when I picked up the New Year's issue of a respected magazine. Proponents of big government have long advocated a revolution in our health care system; the views of big labor are no news. If *Fortune* magazine reflects the point of view of responsible management, here is what the “private sector” now thinks:

“American medicine, the pride of the nation for many years, stands now on the brink of chaos. . . . The time has come for radical change. . . . If they want to guide its direction, physicians must quickly begin to supply some leadership.”

Let us guide the direction of change in the seventies.

### DYSLEXIA PROBLEMS

“I see suddenly a revival of the theory that eye problems are the cause of dyslexia. I see eye exercises being offered as panaceas to cure people with reading disabilities. . . .

“I consider most dyslexia problems to be psychological; of that, there's no question. . . . These youngsters have some form of block; and the harder they try, the worse it becomes. As ophthalmologists, we must tell the parents that to help their child, they must act, after his fiftieth consecutive failure, as though it were his first. If they don't, they're going to tie him up worse than ever. Many of these children will get along all right if we don't push them. In addition some children are not ready to read as early as others; helping them demands even more patience and time to let them grow up a little.”

—ALBERT E. SLOANE, M.D., Boston

Extracted from *Audio-Digest Ophthalmology*, Vol. 7, No. 1, in the Audio-Digest Foundation's series of tape-recorded programs.

## Continuing Medical Education

# Qualifications for CMA's Certificate For Physicians

RONALD L. KAYE, M.D., *Palo Alto*

IN THE FEBRUARY, 1970, issue of CALIFORNIA MEDICINE, background information pertinent to the California Medical Association's Certificate in Continuing Medical Education was published. This formal Certificate in Continuing Medical Education received final approval from the House of Delegates at its meeting in March and will be implemented this fall. A booklet explaining the program and detailing the ways in which CMA will help the physician maintain a record of those educational activities which qualify him for certification will be distributed in August.

The certificate will formally acknowledge the accomplishments of California physicians who keep pace with advancing medical knowledge. The program, a reflection of the medical profession's traditional concern with the quality of medical care, recognizes that the profession itself is best qualified to assess the adequacy of the continuing medical education of California physicians. The certification program represents a flexible approach permitting constant modification. It encompasses continuing medical education of all types; and it anticipates that as new modes of

education are developed, tested and approved, they will be included.

Requirements for the certificate are flexible enough to permit participation by any physician in California engaging in whatever combination of continuing medical education activities is consistent with his particular professional setting.

Certification will be awarded for three consecutive years of accredited or approved educational activities. During this three-year period a total of 200 hours of time is required for certification. The program has established two categories of educational activities, "Required" (Group A), and "Elective" (Group B). As can be seen in the graphic summary a minimum of 75 hours of the 200-hour total must be from the Group A category, although all of the 200 hours may be from Group A. Fifteen hours of Group A credit must be completed within each given year for that year to count toward certification. The certificate is to be awarded for consecutive qualifying years, as the emphasis is on continuing and not sporadic medical education.

Eligibility is extended to any California licensee, whether a member of CMA or not, as well as to any physician member of the Armed Forces, Veterans Administration or U.S. Public Health Service, provided he resided in California for the three consecutive years in which he participates in his qualifying 200 hours of educational activities.

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The author is the Chairman of the CMA Committee on Continuing Medical Education and Director of Medical Education, Palo Alto Medical Clinic.

Submitted April 15, 1970.

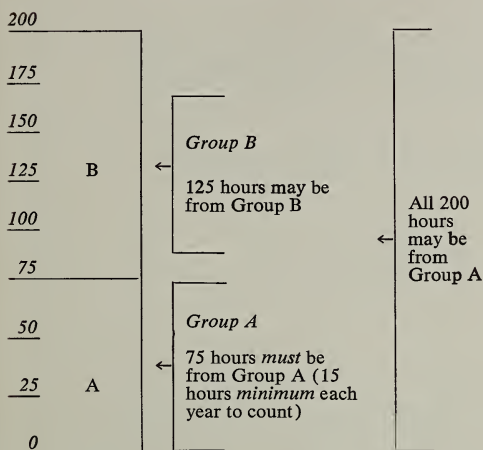
Reprint requests to: CMA Committee on Continuing Medical Education, 693 Sutter Street, San Francisco, Ca. 94102.



## GRAPHIC SUMMARY

### Number of Hours of Continuing Education Activities for Certification in Three Years

Total: 200 hours in three years



"Required" (Group A) activities include: Any accredited, formally constituted meeting, program or course sponsored by medical schools, medical institutions, specialty societies, and voluntary health agencies; teaching, publications, and research activities; presentation of papers and educational exhibits at a recognized medical meeting; and any other learning experience which an in-

dividual physician or medical group considers meritorious for which accreditation has been received by advance application.

"Elective" (Group B) activities include: Attendance and teaching activities at other medical meetings, programs, courses, and grand rounds not included in Group A; individual reading of journals and journal clubs; audio and/or visual medical programs; attendance at postmortem with pathologist and other activities for which accreditation has been received by advance application.

The physician participating in the Certification Program will be asked to keep a detailed record of his continuing medical education activities and to submit his records annually for review by the California Medical Association. As earlier announced there will be a mechanism for California physicians to obtain the AMA Physician's Recognition Award by reciprocity, to avoid duplication of record keeping.

The California Committee on Continuing Medical Education (CCCME) will contact county medical society presidents and executive secretaries, hospital chiefs of staff and directors and individual physicians this summer. Following these initial contacts a booklet will be sent to each individual physician, detailing and elaborating on the program and providing forms for the physician to maintain a record of those educational activities which qualify him for certification.

At this time the CMA Committee on Accreditation is establishing criteria for inclusion of institutions and educational activities in the program. The Evaluation Subcommittee of our CCCME committee has formulated a booklet to be sent to all hospitals to help with educational programs and activities. It is anticipated that at some point in the future educational programs will be developed based on physician need and that these needs will reflect requirements necessary for the continued high quality care of our patients—a prime goal of this Certification Program.

## ERIN GO BAWL

"An Irish pediatrician friend of mine . . . tells how he examines newborns who are crying and making his examination difficult. Instead of making the usual cooing, mothering noises, he actually counters the infant with a cry as loud and ferocious as the infant is making. More often than not, the infant stops crying. You can imagine this large Irishman leaning over a small infant and the consternation among the nursing staff when he makes this noise at the baby. He's now demonstrated this repeatedly, he's recorded it, and he's written a small paper about it."

—FREDERICK RICHARDSON, M.D., Baltimore  
Extracted from *Audio-Digest Otorhinolaryngology*, Vol. 2, No. 6, in the Audio-Digest Foundation's subscription series of tape-recorded programs.

# Clinical Laboratory Personnel

## Is There a Shortage in California?

JEAN PUFFER, B.S., M.P.H., LUCILE GREEN, B.S., M.P.H., AND  
HOWARD L. BODILY, Ph.D., Berkeley

■ *In a study of vacancy rates for laboratory personnel in California to determine if there is in fact a serious or critical shortage of qualified individuals in this group of allied health professionals, it was found that while the answer is still elusive, it would appear that although the shortage may be somewhat greater than normal it is not critical in most areas of the state.*

*For most areas, the situation seems to have improved from 1966 to 1968. There are a few geographical areas, predominantly rural, where shortages of licensed personnel are critical. Vacancy rates also are higher in hospital laboratories. Recruitment difficulties in these situations may be related to insufficient incentives, including but not necessarily limited to salaries.*

*Training in California laboratories may facilitate recruitment in specific instances, and may assume greater importance in the future as working conditions for health professionals continue to improve in other states. And finally, the use of laboratory assistants, aides, and clerks can materially assist the laboratory work, thereby freeing the licensed professional staff to accept responsibilities commensurate with the increasing sophistication of laboratory knowledge and practice.*

IN CALIFORNIA TODAY there are approximately 1,600 clinical laboratories. Half of them are located in the more populous southern area of the state; the remainder either are clustered in the San Francisco Bay and Central Valley regions, or

are scattered in the rural areas of the northern part of the state. All of these medically oriented laboratories operate under permit from the California State Board of Health.

Two-thirds of the laboratories providing services to California's physicians are located in buildings outside of hospital facilities; the remaining third are an integral part of the state's 500 hospitals. The majority are directed by licensed physicians

From Laboratory Services, California State Department of Public Health, Berkeley.

Submitted October 3, 1969.

Reprint requests to: Laboratory Services, State of California, Department of Public Health, 2151 Berkeley Way, Berkeley, Ca. 94704 (Jean Puffer).

and surgeons, mainly pathologists; 15 percent, however, are directed by licensed bioanalysts. The laboratories vary in size from small facilities employing part-time personnel to a large hospital laboratory with a staff of more than a hundred. Almost half employ only a single full-time clinical laboratory technologist. Professional personnel exclusive of physicians (bioanalysts, clinical laboratory technologists, and trainees) are licensed by the Board of Health; other technical assistants and clerks are unlicensed.

Data previously obtained on clinical laboratory manpower supply and needs in California have indicated that there has been a lessening of the shortage of personnel.<sup>1,2</sup> This information is contrary to the commonly held belief that a critical shortage currently exists.<sup>3</sup> A survey was conducted by the Department of Public Health, Laboratory Services, in 1966 and repeated in 1968 to determine if any substantial change had occurred in California as expressed by the national experience or as a result of the implementation of Medicare and Medi-Cal. An attempt was made to assess the influence of various factors on employment and on the supply of personnel.

Procedure

In May 1966 a questionnaire was sent to each licensed clinical laboratory requesting information regarding the number of budgeted positions, both full-time and part-time, for clinical laboratory technologists, laboratory assistants, trainees and clerks, but excluding the laboratory director; the number of vacancies in these budgeted positions; the average length of time these positions remained vacant; and the reasons for leaving employment. A follow-up questionnaire was sent one month later to those laboratories which had not respond-

ed to the first mailing. Additional information on whether the laboratory offered an approved training program in clinical laboratory technology was obtained concurrently from department files.

In May 1968 questionnaires seeking essentially the same information were again sent to all laboratories. Additional information on training laboratories was not obtained.

Since much of the information gathered in these two surveys is repetitious, only differences or change are stressed in this paper. In most instances the 1966 data are presented because the original analysis was somewhat more detailed than that obtained in 1968.

Results

Response to the 1966 and 1968 surveys as measured by rate of return of the questionnaire was 92 percent. Slightly more hospital laboratory directors returned questionnaires than did directors of non-hospital laboratories. The response from laboratories with training programs was close to 100 percent.

Staffing California laboratories are approximately 11,000 professional, technical, and clerical personnel exclusive of the laboratory director. Although there was little change in the number of laboratories between 1966 and 1968, the increase in the number of laboratory positions was 19 percent. However, it is apparent from Table 1 that while there was only a moderate increase (14 to 15 percent) in the number of technologist positions, there was a 20 to 30 percent increase in the number of jobs for unlicensed laboratory assistant and clerical personnel.

In 1966 the overall vacancy rate for all classifications of positions in the responding laboratories was 7 percent (Table 1). By 1968 the overall va-

Number of Budgeted Laboratory Positions and Vacancies Reported by Classification of Position in California—May 1966 and May 1968

Classification of Position	Total Budgeted Positions			Vacant Positions			
	Number		% Change 1966-68	Number		Percent	
	1966	1968		1966	1968	1966	1968
Total	9,881	11,784	+19	659	630	7	5
Clinical Lab. Technologist							
Full-Time	4,566	5,200	+14	357	305	8	6
Part-Time	1,554	1,786	+15	124	125	8	7
Laboratory Assistant							
Full-Time	996	1,323	+33	23	24	2	2
Part-Time	604	727	+20	27	14	4	2
Clerk							
Full-Time	1,199	1,587	+32	22	46	2	3
Part-Time	438	556	+21	7	13	2	2

TABLE 1



*Number and Percent Distribution of Hospital and Non-Hospital Laboratories by Size in California — May 1966  
(Size Based on Number of Budgeted Full-Time Technologist Positions)*

	Size of Laboratory (Number of Technologist Positions)	Number of Laboratories			Percent Distribution		
		All	Hospital	Non-Hospital	All	Hospital	Non-Hospital
TABLE 2	Total .....	1,218*	493	725	100	100	100
	1 .....	543	107	436	45	22	60
	2 .....	234	92	142	19	19	20
	3-5 .....	254	140	114	21	28	16
	6-10 .....	90	70	20	7	14	3
	11-19 .....	59	54	5	5	11	†
	20+ .....	30	30	4	2	6	†
	Not stated .....	4	..	4	†	..	†

\*Excludes 126 laboratories reporting only part-time technologist positions.  
†Less than one percent.

cancy rate was 5 percent. Within this group, however, the rates for laboratory assistant and clerical positions were low (2 to 4 percent) in 1966, and remained low in 1968. Vacancy rates for clinical laboratory technologist positions were higher than those for nonprofessional classifications in both 1966 and 1968 (8 percent and 6 percent, respectively). These figures suggest a decrease in the vacancy rate for technologist positions during the intervening two years. If such a decrease continues, it could assume more significance than it has now.

The responding laboratories were classified by type as hospital or non-hospital and by "size" to determine if these factors affected the vacancy rates. Although size could be defined in a number of different ways, for the purpose of this study it was assumed that the number of budgeted full-time technologist positions most nearly reflected workload and thus represented size.

Of a total of 1,344 laboratories responding in the 1966 survey, 1,218 (91 percent) reported having at least one or more budgeted full-time clinical laboratory technologist positions (Table 2). Almost half of these 1,218 laboratories (543) have only one budgeted full-time technologist position and most are located outside of hospital fa-

cilities. In contrast, the hospital laboratories vary considerably in size, with well over half of them employing more than three technologists.

There were some differences reported in vacancy rates between hospital and non-hospital laboratories (Table 3). In 1966, the overall vacancy rate for full-time technologists was 8 percent, with hospitals reporting 9 percent and non-hospitals 6 percent. Rates in laboratories of varying sizes ranged from 2 percent in the one-technologist non-hospital laboratories to 10 percent in one-technologist hospital laboratories and medium-sized (three to five technologists) non-hospital laboratories. It would appear that vacancy rates in hospital laboratories were somewhat higher than in laboratories outside hospitals. Except in the one-technologist non-hospital laboratories, size of laboratory alone does not seem to affect the vacancy rates. Since vacancy rates for 1968 were lower than for 1966, further attempts to evaluate the effect of size of laboratory on the rate did not seem warranted.

Another factor affecting vacancies might be the presence or absence of a training program. Training of clinical laboratory personnel in California occurs primarily in hospital laboratories. One-third of hospital laboratories (185 of 535) reporting in 1968 were training laboratory personnel. In

*Number of Budgeted Full-Time Technologist Positions and Percent Vacant in Hospital and Non-Hospital Laboratories  
By Size of Laboratory in California—May 1966*

	Size of Laboratory	Number of Positions			Percent Vacant		
		All	Hospital	Non-Hospital	All	Hospital	Non-Hospital
TABLE 3	Total .....	4,566	3,104	1,462	8	9	6
	1 .....	543	107	436	3	10	2
	2 .....	468	184	284	6	7	6
	3-5 .....	913	506	407	10	9	10
	6-10 .....	687	541	146	8	9	5
	11-19 .....	871	803	68	9	9	7
	20+ .....	1,074	963	111	8	8	5
	Not stated .....	10	....	....	0	..	..

contrast, less than 10 percent of the non-hospital laboratories were offering training programs. Although only 256 laboratories were training technologists in 1966, most of these laboratories were in hospitals and employed more than half the technologists in the state. The vacancy rate for full-time technologist positions in laboratories with training programs was 8 percent, against a vacancy rate of 7 percent in laboratories with no training programs. In geographical areas where few or no laboratories maintain training programs, vacancy rates tended to be higher than average. However, it is possible that other factors might be more important in recruitment than the presence or absence of a training program (for example, location of the laboratory, movement of personnel to urban areas, salaries). It would appear that the maintenance of training programs does not per se improve recruitment; in fact, survey data suggest that training laboratories are less able to recruit than those that do not train.

As with previous surveys, vacancy rates in 1966 and 1968 varied considerably with geographical location. In 1966, four predominantly rural areas of the state were experiencing vacancy rates of between 10 percent and 15 percent, with a tendency for rates to be slightly higher in the hospital laboratories than in non-hospital laboratories. In 1968, only two geographical locations had rates this high, with 10 percent vacancies in the mountain area and 12 to 15 percent in the central coast area (Table 4). Again hospital laboratories had slightly higher rates than non-hospital laboratories. In most urban areas, rates ranged from 5 to 8 percent, although in the San Francisco Bay region the rates were only 2 to 3 percent.

## Reasons for Leaving Employment

Of 1,355 laboratory directors responding to the questionnaire in 1968, almost two-thirds gave one or more reasons for clinical laboratory technologists leaving employment. By far the most common reason given was change of residence (53 percent), followed by better salary (21 percent), maternity (15 percent), and dismissal. There was some indication that low salaries are a more important factor for leaving employment in hospital laboratories than in non-hospital laboratories.

Response from the laboratories to the question of how long positions remained vacant was rather poor, in that only about one-third stated a definite time interval. In both hospital and non-hospital laboratories positions usually remained vacant from one to four weeks. Most positions were filled in less than two months. Non-hospital laboratories seemed to be more able to recruit within one month than hospital laboratories.

## Discussion

In evaluating the significance of these vacancy rates for California medical laboratory personnel, it would be helpful to make comparisons with the national situation. Although the problems of health resources and manpower needs have received increasing attention during the past few years, information pertinent to the medical laboratory field remains unreliable for several reasons. In the first place, laboratory activities and classifications of personnel are poorly defined and described. Second, most of the information which has been gathered relates only to personnel employed in hospital laboratories.<sup>4</sup> And finally, since

*Number of Budgeted Full-Time Technologist Positions and Percent Vacant in Hospital and Non-Hospital Laboratories By Geographic Area in California—May 1968*

Geographic Area*	Number of Positions			Percent Vacant		
	All	Hospital	Non-Hospital	All	Hospital	Non-Hospital
Total, All Areas	5,200	3,650	1,550	6	6	5
North Coast	36	29	7	3	3	0
Sacramento Valley	256	164	92	7	8	5
Mountain	96	77	19	10	10	10
San Francisco Bay, Total	1,392	1,029	363	3	3	2
SF-Oakland Metropolitan	978	743	235	3	3	2
San Jose Metropolitan	355	249	106	2	3	1
North Central Coast	59	37	22	2	0	4
Central Coast	98	68	30	12	15	7
San Joaquin Valley	356	224	132	7	7	6
Santa Barbara-Ventura	131	93	38	8	8	10
Los Angeles Metropolitan	2,275	1,553	722	7	8	7
San Diego Metropolitan	293	214	79	1	1	0
Southeast	267	199	68	7	8	1

\*California State Statistical Areas, Interdepartmental Research Coordinating Committee.



there has been no mechanism for determining how many persons are currently working in clinical laboratories, national projections are fragmentary.<sup>5,6,7</sup> The most widely quoted estimate of laboratory personnel in 1967 was a total of 100,000 individuals, including 4,000 baccalaureate laboratory scientists, 40,000 technologists registered with the American Society of Clinical Pathologists, and 56,000 non-registered laboratory personnel.<sup>8</sup> Even manpower studies specifically relating to laboratories<sup>9,10,11</sup> provide limited information on the extent of personnel shortages or turnover either nationally or within the states.

In California there have been concerted efforts to study and appraise manpower problems in the health services. During the past three years, these efforts have culminated in three health manpower conferences, an allied health conference in July 1968, a survey of educational facilities by the Regional Medical Programs, for formation of a statewide health manpower council, and the organization of committees on health manpower as an integral part of state and local comprehensive health planning programs.

In a recent study by the Health Manpower Council of California<sup>12</sup> a sampling of 194 or 40 percent of California's 518 hospitals was undertaken through interviews. The vacancy rate for all health personnel in these hospitals was 4.5 percent, with a range of zero to 14 percent in different areas of the state. For licensed full-time clinical laboratory technologists in these hospitals and in 15 out of a total of approximately 900 private laboratories, the vacancy rate was 4.5 percent, with a range of zero to 54 percent. In reporting these figures at the Health Manpower Conference held December 3, 1968 in San Diego,<sup>13</sup> Kenneth Briney, executive director of the Council, cautioned participants that although his figures showed considerable variation between geographic locations, it was not correct to conclude that recruitment problems were limited only to rural areas. He emphasized that distribution of health personnel within counties was also uneven. Results obtained in this current study on laboratory personnel support his conclusions. Another point stressed by Mr. Briney in relation to registered nurses, but also apparent in other manpower data relating to physicians,<sup>14,15</sup> is that California is a "debtor" state—that is, most of the health professionals taking California licensing examinations are from other states. The same situation is also true for clinical

laboratory technologists, in that almost two-thirds of those licensed in 1968 received their academic training and bench experience outside California.

In explaining the reasons for employees' leaving one job to seek another, Berenson<sup>16</sup> concluded that poor work assignments, poor management, obsolete knowledge, misunderstood expectations, poor job induction and low job interest are important factors. These elements no doubt contribute to decisions to "change residence," a factor so prominent in the present study as a reason for leaving employment. However, it is tempting to speculate that the mobility of laboratory personnel in California is based mainly on personal reasons, as demonstrated by the fact that maternity and marriage, as well as change of residence, are frequently mentioned in the survey.

This pattern of mobility suggests that the rate of turnover among laboratory personnel is high. Since the present study was not designed as a continuous monitoring system, it sheds no light on the extent of this problem. However, departmental personnel records show that although approximately 1,000 new clinical laboratory technologist licenses are issued a year and 11,000 are renewed, the net gain in licensed personnel from year to year is less than 600.<sup>17</sup> Attrition is close to 40 percent as laboratory personnel leave the field or become inactive. In view of the fact that technologist vacancies average 500 per year, the reservoir of professional manpower would appear to be barely adequate. However, the fact that there are 11,000 licensed technologists for approximately 8,000 budgeted positions would suggest a favorable recruitment situation.

A final problem in evaluating the significance of a 6 percent vacancy rate for clinical laboratory technologists is lack of agreement as to what figure represents a "serious" or "critical" shortage. The 8 percent vacancy rate existing in 1966 was considered in our earlier study as "representing no shortage."<sup>2</sup> Department of Employment officials consider a 2 to 3 percent vacancy rate in industry as no shortage or "normal"; beyond this figure, there apparently are no published guides as to what constitutes various gradations of shortages. The Health Manpower Council of California has suggested 2 to 3 percent as normal, 3 to 8 percent as borderline to serious (depending on the group and type of work), and greater than 10 percent as critical. According to these criteria, the situation in California laboratories in 1968 is



critical in only two geographical areas, borderline to serious in five, and essentially normal in six. Yet, to the concerned laboratory director any vacancy at all may represent a critical shortage. He may find himself limited in what he can offer as financial inducement to prospective technologists, and may try to solve his problem by hiring persons with lesser technical and professional qualifications. Although by law these unlicensed people cannot perform clinical laboratory tests in California, they often can carry out essential tasks related to preparation of specimens and reagents, record keeping, equipment monitoring, and maintenance. Possibly the 20 to 30 percent increase in non-licensed personnel from 1966 to 1968, as against the 15 to 18 percent increase in licensed technologists, could be explained by assuming such a solution to the recruiting problem.

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# In Memoriam

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Persons wishing to do so may make contributions to the Physicians' Benevolence Fund to honor the memory of a member who has died. Members of the family will be notified that such a contribution has been made and the name of the donor will be supplied.

Checks should be addressed to Physicians' Benevolence Fund, Inc., California Medical Association, 693 Sutter Street, San Francisco, Ca. 94102.

ALTER, SAMUEL MITCHELL, Los Angeles. Died April 6, 1970 in Los Angeles of gastric hemorrhage, aged 81. Graduate of Harvard Medical School, Boston, 1912. Licensed in California in 1912. Doctor Alter was a member of the Los Angeles County Medical Association.

BERG, FRANCIS, San Francisco. Died January 12, 1970 in San Diego, aged 69. Graduate of Deutsche Universität Medizinische Fakultät, Prague, 1924. Licensed in California in 1950. Doctor Berg was a retired member of the San Francisco Medical Society and the California Medical Association, and an associate member of the American Medical Association.

CRAIG, R. GLENN, San Francisco. Died February 20, 1970 in San Francisco, aged 72. Graduate of Johns Hopkins University School of Medicine, Baltimore, 1922. Licensed in California in 1928. Doctor Craig was a member of the San Francisco Medical Society.

HARTWIG, W. RAY, Bishop. Died February 22, 1970 in Los Angeles of cancer, aged 44. Graduate of University of Southern California School of Medicine, Los Angeles, 1958. Licensed in California in 1959. Doctor Hartwig was a member of the Inyo-Mono County Medical Society.

JACOBI, DONALD E., San Francisco. Died March 5, 1970 in San Francisco, aged 36. Graduate of University of Michigan Medical School, Ann Arbor, 1957. Licensed in California in 1963. Doctor Jacobi was a member of the Alameda-Contra Costa Medical Association.

KLASSEN, PAUL LEONARD, Burbank. Died April 2, 1970 in Glendale of malignant brain tumor, aged 46. Graduate of University of Southern California School of Medicine, Los Angeles, 1948. Licensed in California in 1948. Doctor Klassen was a member of the Los Angeles County Medical Association.

KRAFT, ROLLAN WALTER, Altadena. Died March 2, 1970, aged 79. Graduate of University of Michigan Medical School, Ann Arbor, 1915. Licensed in California in 1920. Doctor Kraft was a retired member of the Los

Angeles County Medical Association and the California Medical Association, and an associate member of the American Medical Association.

LAPIN, SAMUEL B., Glendale. Died April 4, 1970 in Glendale of coronary occlusion, aged 58. Graduate of Hahnemann Medical College and Hospital of Philadelphia, 1934. Licensed in California in 1946. Doctor Lapin was a member of the Los Angeles County Medical Association.

MATHISON, NELSON E., Long Beach. Died April 12, 1970 in Norwalk of bronchopneumonia with cerebral arteriosclerosis, aged 58. Graduate of College of Osteopathic Physicians and Surgeons, Los Angeles, 1937. Licensed in California in 1937. M.D. degree from California College of Medicine, 1962. Doctor Mathison was a member of the Los Angeles County Medical Association.

SLEPNIKOFF, STEVAN FREDERICK, Madera. Died March 5, 1970 in Madera of heart disease, aged 61. Graduate of College of Medical Evangelists, Loma Linda-Los Angeles, 1936. Licensed in California in 1936. Doctor Slepnikoff was a member of the Fresno County Medical Society.

SOOY, DANIEL WARREN, Los Angeles. Died March 11, 1970 in Los Angeles, aged 83. Graduate of the University of California Medical School, Berkeley-San Francisco, 1917. Licensed in California in 1917. Doctor Sooy was a member of the Los Angeles County Medical Association.

TANDY, WILLIAM, Los Angeles. Died March 28, 1970 in Los Angeles of cardiac failure, aged 66. Graduate of the Ohio State University College of Medicine, Columbus, 1934. Licensed in California in 1943. Doctor Tandy was a member of the Los Angeles County Medical Association.

THOMASON, SIDNEY DALE, Claremont. Died March 31, 1970 in Pomona of multiple myeloma, aged 72. Graduate of Northwestern University Medical School, Chicago, 1926. Licensed in California in 1926. Doctor Thomason was a member of the Los Angeles County Medical Association.

TONGE, ARCHIE N., Modesto. Died February 21, 1970 in Modesto, aged 74. Graduate of the College of Medical Evangelists, Loma Linda-Los Angeles, 1924. Licensed in California in 1924. Doctor Tonge was a member of the Stanislaus County Medical Society.

VANCE, ROBERT WILLIAM, San Diego. Died March 26, 1970, aged 66. Graduate of Northwestern University Medical School, Chicago, 1929. Licensed in California in 1939. Doctor Vance was a retired member of the San Diego County Medical Society and the California Medical Association, and an associate member of the American Medical Association.



# PUBLIC HEALTH REPORT

Louis F. Saylor, M.D., M.P.H., Director, State Department of Public Health

## Nitrates in California's Water

SINCE 1945, WHEN NITRATE in a ground water supply in Minnesota was identified as a potential health hazard in that it was a cause of methemoglobinemia in infants, the California State Department of Public Health has kept close surveillance on community water supplies. Water purveyors with sources high in nitrate were requested to make routine analyses and to reduce nitrate concentrations in delivered water by abandoning or blending such sources with low nitrate water and using the wells only in event of water shortage.

In 1962, for the first time, a nitrate limit was included in the Public Health Service Drinking Water Standards. This nitrate standard appears as a recommended limit that should not be exceeded in a domestic water supply "when other more suitable supplies are or can be made available." The standard also includes a footnote: "In areas in which the nitrate content of water is known to be in excess of the listed concentration ( $\text{NO}_3$ —45 mg per liter), the public should be warned of the potential dangers of using water for infant feeding." In 1967, the State Health Department established administrative procedures to be followed when public water supplies did not meet the USPHS Drinking Water Standards. These procedures include the provision that when nitrates exceed 90 mg per liter the local health officer will advise physicians practicing in the community of the problem and the risks involved.

In 1968, the California Department of Water Resources conducted a study in the Delano area of Kern County and found that nitrates were present in highest concentration in areas where the ground water table has risen considerably during recent years, where soils of high permeability require greater use of irrigation water, or where irrigation has been practiced over long periods. It was demonstrated that the source of excessive nitrate lay above the water table. Domestic sewage was excluded as a major source of nitrate.

At present, there are several areas in the state where the nitrate content in water supplies has exceeded or on occasion does exceed the 45 mg per liter standard. These areas are the Arroyo Grande-Grover City area, the foothills of the San Gabriel Mountains, the West County Basins of San Bernardino County and Riverside County, and the Delano and Porterville areas.

Although there have been no reported cases of methemoglobinemia in infants using public water supplies in the State of California, there has been considerable interest and concern regarding the possibility of subclinical health effects. In November 1969, Senate Bill No. 1387, which was introduced by Senator Stiern of Kern and Kings counties, authorized and appropriated funds for a one-year State Health Department study of infants in the Delano area. An interdisciplinary planning group was established to develop a research protocol and conduct studies in that area.

The study efforts are being directed toward the more susceptible group, infants under three months of age. The hypotheses are that their fetal hemoglobin may be more easily oxidized, that there is a deficiency of red cell enzymes, and that the stomach pH permits bacteria to grow. With a source of nitrate from water, medicine or food, the bacteria may convert nitrate to nitrite, which is absorbed into the blood and converts hemoglobin



to methemoglobin and, consequently, interferes with the oxygen-carrying capacity of the blood. Symptoms of clinical effects of this process in infants are cyanosis and respiratory difficulty.

The study has been developed to determine if nitrates in the water could affect the health of the infants. Through agreement and discussion with local physicians and the local health department, all mothers of infants born in the area are invited to attend special clinics. During an interview, the food and water intake of the infant during the preceding 24 hours is determined and a specimen of capillary blood is taken from the infant for hemoglobin and methemoglobin analysis, which must be completed within 45 minutes of collection. In addition the home is visited to collect samples of the family water supply and of the water and formula consumed by the infant. All water samples are tested for nitrate immediately and are then sent to the state laboratory in Berkeley for routine bacteriological and other chemical analyses, including nitrite ion. From these data,

a fairly accurate estimate of the nitrate and nitrite consumption per kilogram of body weight can be determined and related to the methemoglobin content of the blood. If the methemoglobin is elevated, the test is repeated and a medical examination is done on the child from whom the specimen was obtained, as well as a control child to determine if there are differences in the general health status.

The cities of Delano and McFarland are collecting weekly water samples from operating wells and the Kern County Health Department is assisting in various ways, including providing a sanitarium to help in the collection of home samples. The community and families have been very cooperative and are interested in the project.

The findings will be reviewed and evaluated regularly. At the end of the year an analysis of the data should allow us to make some decision as to the existing levels of nitrate in the water supply and as to whether these levels represent a health problem to infants.

### TESTING THE BATTERIES IN PACEMAKERS

"We think that x-ray studies are very helpful in assessing the battery charge on a pacemaker. Most physicians who have any series of patients with pacemakers find it advisable to have some kind of a pacemaker clinic or follow-up regularly, that is, they don't wait until patients have trouble. The patients come in about every 3 or 6 months, at which time it's easy to take an x-ray with a special technique—no special machine—just special exposure factors. At least with the Medi-Tronics and General Electric pacemakers, the batteries are oriented in such a fashion that one can assess the state of charge. The basis of this is simply that in the charged state the mercury is in the form of mercuric oxide. As the battery discharges, metallic mercury is deposited. . . . This has been helpful in detecting the need for replacement before the unit actually fails. . . . It also seems a little more sensible than just taking an arbitrary time, such as two years, for replacing the cells."

—C. WALTON LILLEHEI, M.D., New York City  
Extracted from *Audio-Digest Internal Medicine*, Vol. 16, No. 3, in the Audio-Digest Foundation's subscription series of tape-recorded programs.

# CONTINUING MEDICAL EDUCATION ACTIVITIES IN CALIFORNIA AND HAWAII

(FORMERLY WHAT GOES ON)

## COMMITTEE ON CONTINUING MEDICAL EDUCATION

THIS BULLETIN of information regarding continuing education programs and meetings of various medical organizations in California and Hawaii is supplied by the Committee on Continuing Medical Education of the California Medical Association. In order that they may be listed here, please send communications relating to your future meetings or postgraduate courses to Committee on Continuing Medical Education, California Medical Association, 693 Sutter Street, San Francisco 94102; or phone: (415) 776-9400, extension 241.

## ALCOHOLISM AND DRUG USE

September 19-20—**Drug Abuse.** UCSF. Saturday-Sunday.

October 3-4 — **Drugs and Other Addictions.** UCSF at Napa State Hospital, Imola. Saturday-Sunday.

## MEDICINE

June 15-July 3—**Coronary Care for Physicians Training Program.** CRMP Area IV and Cedars-Sinai Medical Center at Cedars of Lebanon Hospital, Los Angeles. Three week course repeated six times through November, designed for practicing internists or cardiologists who will subsequently be working in or directing CCU in community hospitals. Electrocardiography, physical diagnosis, CCU planning and administration, electrolytes and acid-base metabolism, emphasis on practical techniques. Contact: Herbert Stein, M.D., Coronary Care for Physicians Training Programs, Dept. of Cardiology, Cedars of Lebanon Hospital, Box 54265, Los Angeles 90029. (213) 662-9111, ext. 306.

June 17-18—**Exercise in Coronary Disease.** USC at Rancho Los Amigos Hospital, Downey. Wednesday-Thursday. 12 hrs.

June 22-23—**American Diabetes Association—Annual Meeting Scientific Sessions.** Sheraton-Palace Hotel, San Francisco. Monday-Tuesday. Contact: J. Richard Connelly, Exec. Dir., 18 E. 48th Street, New York 10017. (212) 752-8550.

July 5-16 — **Coronary Care Unit Program for Physicians.** CRMP Area V at Los Angeles County-USC Medical Center. Two week course repeated monthly. Arrhythmia detection, diagnosis and therapy, defibrillation and cardioversion, central venous pressure monitors, placement of pacing catheters, new aspects in diagnosis and treatment of congestive heart failure, shock and associated respiratory problems, and CCU management in community hospitals. Contact: Gladys Ancrum, Dr. P. H., Administrative Associate, CRMP

Area V, 1 West Bay State St., Alhambra 91801. (213) 576-1626.

August 16-19—**The Thirteenth Annual Advanced Seminar on Internal Medicine.** UCLA at UCLA Residential Conference Center, Lake Arrowhead. Sunday-Wednesday.

September 14-18—**Internal Medicine.** UCSF and the American College of Physicians at UCSF. Monday-Friday.

September 14-October 2—**Coronary Care for Physicians Training Program.** See Medicine, June 15-July 3.

September 16 — **Tenth Annual Kidney Disease Symposium.** Kidney Foundation of Southern California at Ambassador Hotel, Los Angeles. Wednesday. \$25. 8 hrs. Contact: Leonard Gottlieb, Exec. Dir., KFSC, 5880 San Vicente Blvd., Los Angeles 90019. (213) 936-5529.

## KEY TO ABBREVIATIONS AND SYMBOLS

Medical Centers and CMA Contacts  
for Information

- CMA:** California Medical Association  
Contact: Continuing Medical Education, California Medical Association, 693 Sutter Street, San Francisco 94102. (415) 776-9400, ext. 241.
- LLU:** Loma Linda University  
Contact: John E. Peterson, M.D., Associate Dean for Continuing Medical Education, Loma Linda University School of Medicine, Loma Linda 92354. (714) 796-7311.
- PMC:** Pacific Medical Center  
Contact: Arthur Selzer, M.D., Chairman, Education Committee, Pacific Medical Center, Clay and Webster Streets, San Francisco 94115. (415) 931-8000.
- STAN:** Stanford University  
Contact: John L. Wilson, M.D., Chairman on Postgraduate Education, Stanford University School of Medicine, 300 Pasteur Drive, Stanford 94305. (415) 321-1200, ext. 5594.
- UCD:** University of California, Davis  
Contact: George H. Lowrey, M.D., Professor and Chairman, Department of Postgraduate Medicine, University of California, Davis, School of Medicine, Davis 95616. (916) 752-0331.
- UCI:** University of California — California College of Medicine, Irvine  
Contact: Robert Combs, M.D., Associate Dean, University of California, Irvine—California College of Medicine, Irvine 92664. (714) 833-5991.
- UCLA:** University of California, Los Angeles  
Contact: Donald Brayton, M.D., Associate Dean and Head, Continuing Education in Medicine and the Health Sciences, 15-39 Rehabilitation Center, UCLA Center for the Health Sciences, Los Angeles 90024. (213) 825-6514.
- UCSD:** University of California, San Diego  
Contact: Michael Shimkin, M.D., Associate Dean for Health Manpower, 1309 Basic Sciences Building, University of California, San Diego, School of Medicine, La Jolla 92037. (714) 453-2000, ext. 2704.
- UCSF:** University of California, San Francisco  
Contact: Seymour M. Farber, M.D., Dean, Educational Services and Director, Continuing Education, Health Sciences, University of California Medical Center, San Francisco 94122. (415) 666-1692.
- USC:** University of Southern California  
Contact: Phil R. Manning, M.D., Associate Dean, Postgraduate Division, University of Southern California School of Medicine, 2025 Zonal Avenue, Los Angeles 90033. (213) 225-1511, ext. 203.



September 19 — **Asthma — Adult and Child.** UCSF at Childrens Hospital and Adult Medical Center, San Francisco. Saturday.

September 19—**Fourteenth Annual Symposium on Cardiovascular Disease.** Santa Barbara and Ventura Counties Heart Associations at Biltmore Hotel, Santa Barbara. Saturday. \$15. 6 hrs. Contact: Mrs. Sara Clyde, Exec. Dir., SBCHA, 18 La Arcadia Ct., Santa Barbara 93103. (805) 963-1541.

September 21-October 2—**Intensive Review of Internal Medicine.** USC at Los Angeles County-USC Medical Center, Los Angeles. Two weeks.

September 25-26—**Arthritis.** UCSF. Friday-Saturday.

September 25-26 — **Cutaneous Manifestation of Systemic Disease.** STAN. Friday-Saturday. Contact: Eugene M. Farber, M.D., Dept. of Dermatology, STAN.

October 5-16—**Coronary Care Unit Program for Physicians.** See Medicine, July 5-16.

October 7-9—**Fortieth Annual Physicians' Symposium on Heart Disease.** San Francisco Heart Association at St. Francis Hotel, San Francisco. Wednesday-Friday. \$35. 18 hrs. Contact: Mrs. Frances MacKinnon, Director, Professional Education, SFHA, 259 Geary St., Room 300, San Francisco 94102. (415) 982-5753.

October 14-18 — **Advanced Seminar in Dermatology.** UCLA at El Mirador Hotel, Palm Springs. Wednesday-Sunday.

October 16-17—**Pediatric Nephrology.** UCSF. Friday-Saturday.

October 16-17—**Physical Medicine and Rehabilitation.** UCSF. Friday-Saturday.

October 17—**Liver Disease.** PMC. Saturday.

October 22-25 — **California Society of Internal Medicine: 1970 Annual Meeting.** Del Monte Hyatt House, Monterey. Thursday-Sunday. \$10 nonmembers. 10 hrs. Contact: Cynthia Bell, Exec. Sec., CSIM, 350 Post St., San Francisco 94108. (415) 362-1548.

October 25-30—**American College of Chest Physicians.** Century Plaza Hotel, Los Angeles. Sunday-Friday. Contact: Alfred Soffer, M.D., Exec. Dir., ACCP, 112 E. Chestnut St., Chicago 60611. (312) 787-4933.

Continuously—**Basic Home Course in Electrocardiography.** One year postgraduate series, ECG interpretation by mail. Physicians may register at any time. \$100 (52 issues). Contact: USC.

Continuously—**Training in the Procedure of Tonometry.** Northern California Society for the Prevention of Blindness at the Glaucoma Screening Clinic, San Francisco. Weekly Saturday morning program in tonometry for internists and general practitioners. Advance appointment required, no charge. 3 hrs. Contact: Frederic S. Weisenheimer, Ed.D., Exec. Dir., NCSBP, 4200 California Street, San Francisco 94118. (415) 387-0934.

Continuously — **Medico-Surgical Cardiovascular Seminar.** Palo Alto Veterans Administration Hospital, Palo Alto. First Thursday of each month, lectures, demonstrations, seminar discussions, and rounds. Designed

specifically for a selected group of physicians from the Fresno area. Other physicians invited to participate. Contact: William Angell, M.D., Division of Cardiovascular Surgery, Dept. of Surgery, Palo Alto V.A. Hospital, 3801 Miranda Avenue, Palo Alto 94306. (415) 326-5600.

Continuously—**Coronary Care Unit Training for Physicians.** CRMP Area VI and San Bernardino County General Hospital at San Bernardino County General Hospital. Four week courses at monthly intervals, scheduled by arrangement. For practicing physicians working in and directing CCU's. Bedside care, electrocardiography, physical diagnosis, clinical history, therapy, insertion of pacemakers, cardioversion. 160 hrs. Contact: Carl L. Cook, Jr., M.D., San Bernardino County General Hospital, 780 E. Gilbert St., San Bernardino 92404. (714) 885-3411.

Continuously—**Training for Physicians in Nephrology.** CRMP Area VI and LLU at LLU. Courses of four weeks or more available, to be scheduled by arrangement. Bedside conferences, clinical care and management. Hemodialysis, peritoneal dialysis, renal biopsy and kidney transplantation. 160 hrs. Contact: Stewart W. Shankel, M.D., LLU.

Continuously—**Training for Physicians in General Internal Medicine.** CRMP Area VI and LLU at LLU. Four weeks or more, scheduled by arrangement. Bedside and classroom training, practical aspects of clinical care and management. 160 hrs. Contact: LLU.

Continuously—**Training of Physicians in Modern Concepts of Pulmonary Care.** CRMP Area VI, LLU and Riverside General Hospital. Four weeks or more, scheduled by arrangement. Diagnostic and therapeutic methods in medical chest disease, physiological methodology of modern pulmonary care programs, use of new instrumentation in the field. 160 hrs. Contact: George G. Burton, M.D., LLU.

#### **Grand Rounds—Medicine**

##### **Tuesdays**

8:30-10:00 a.m., Assembly Hall, Harbor General Hospital, Torrance. UCLA.

##### **Wednesdays**

10:30-12:00 noon. Auditorium, Medical Sciences Building. UCSF.

11:00 a.m., Room 1645, Los Angeles County-USC Medical Center. USC.

12:30 p.m., Auditorium, School of Nursing, Orange County Medical Center. UCI.

12:30-1:30 p.m., University Hospital, UCSD.

##### **Thursdays**

10:30-12:00 noon, Room 33-105, UCLA Medical Center. UCLA.

##### **Fridays**

8:00 a.m., Courtroom, Third Floor, Kern County General Hospital, Bakersfield. CRMP Area IV.

8:30 a.m., Auditorium, Lebanon Hall, Cedars of Lebanon Hospital, Los Angeles. CRMP Area IV.

Neurology. 10:15 a.m., held alternately at Stanford University Hospital and Neurology Conference Building 7, V.A. Hospital, Palo Alto. STAN.



1st and 3rd Fridays, 11:00 a.m., Auditorium, Brown Building, Mount Sinai Hospital, Los Angeles. CRMP Area IV.

1:15 p.m., Lieb Amphitheater, Timken-Sturgis Research Bldg., La Jolla. Scripps Clinic and Research Foundation.

Rheumatology Grand Rounds. 11:45 a.m., Room 6441, Los Angeles County-USC Medical Center, Los Angeles. USC.

## MENTAL RETARDATION

October 12-23—**Mental Retardation Workshop.** UCLA and Pacific State Hospital, Pomona, at UCLA Neuropsychiatric Institute. Two weeks. For physicians and allied professionals. Causation, symptomatology, care, treatment and management, diagnostic techniques suitable for office practice, parental reactions and intra-family psychopathology, recent research findings. 80 hrs. Contact: UCLA.

## OBSTETRICS AND GYNECOLOGY

June 20—**Therapeutic Abortions.** USC at Los Angeles County-USC Medical Center, Los Angeles. Saturday. Current legal and procedural problems, role of psychiatric evaluation, amniotomies and suction curettage. \$25. 3 hrs.

August 9-12 — **The Third Annual UCLA Seminar on Obstetrics and Gynecology.** UCLA at UCLA Residential Conference Center, Lake Arrowhead. Sunday-Wednesday.

September 17—**Diabetes in Pregnancy.** USC at Los Angeles County-USC Medical Center, Los Angeles. Thursday.

September 24-27—**American College of Obstetricians and Gynecologists—District VIII Meeting.** Newport Inn, Newport Beach. Thursday-Sunday. Contact: Keith C. White, M.D., 911 E. San Antonio Dr., Long Beach 90807. (213) 423-6417.

October 2-3 — **The Office Practice of Obstetrics and Gynecology.** UCSF at Hilton Hotel, San Francisco. Friday-Saturday.

## Grand Rounds—Obstetrics and Gynecology

### Mondays

10-11:30 a.m., Assembly Room, First Floor, Harbor General Hospital, Torrance. UCLA.

### Fridays

8 a.m., Auditorium, Orange County Medical Center. UCI.

## PEDIATRICS

June 19-21—**Southern California Postgraduate Meeting.** Childrens Hospital of Orange County. Friday-Sunday. Neonatology; Genetics and Inborn Errors of Metabolism; Growth and Endocrinology; Gastroenterology and Shock. \$35. 17 hrs. Contact: Merl J. Carson, M.D., Childrens Hospital of Orange County, 1109 W. La Brea, Orange 92668. (714) 538-8831.

June 24-26—**Annual Pediatric Seminar—The First Ten Months of Life.** Childrens Health Center, San Diego. Wednesday-Friday. \$25. 15 hrs. Contact: David L.

Chadwick, M.D., Medical Director, 8001 Frost Street, San Diego 92123. (201) 277-5808.

September 23-24—**Annual Brennemann Memorial Lectures.** Los Angeles Pediatric Society at Sportsmans Lodge, North Hollywood. Wednesday-Thursday. Contact: Mrs. Eve Black, Exec. Sec., LAPS, P.O. Box 2022, Inglewood 90305. (213) 753-3704.

October 3-4—**Health of the School Child.** UCSF. Saturday-Sunday.

October 14—**Newborn Infant Care.** USC. Wednesday. 6 hrs.

October 17-22—**American Academy of Pediatrics.** Hilton Hotel, San Francisco. Saturday-Thursday. Contact: Robert G. Frazier, M.D., Exec. Dir., AAP, 1801 Hinman Ave., Evanston, Ill. 60204. (312) 869-4255.

October 31-November 1—**What Are Potentials for Pre-school Child's Needs?** UCSF. Saturday-Sunday.

## Grand Rounds—Pediatrics

### Tuesdays

8:00 a.m., Childrens Hospital Medical Center, Oakland.

8:30 a.m., Auditorium, Childrens Division Building, Los Angeles County-USC Medical Center, Los Angeles. USC.

8:30 a.m., Room 4-A, Kern County General Hospital, Bakersfield. CRMP Area IV.

8:30 a.m., Pathology Auditorium, San Francisco General Hospital.

### Wednesdays

8-9:00 a.m., held alternately at Auditorium, Orange County Medical Center and Auditorium, Childrens Hospital of Orange County. UCI.

8:30 a.m., Bothin Auditorium, Childrens Hospital, San Francisco.

### Thursdays

8:30-10:00 a.m., Room 664, Science Building, UCSF.

8:30-9:30 a.m., Lebanon Hall, Cedars of Lebanon Hospital, Los Angeles.

8:30 a.m., First Floor Auditorium, Harbor General Hospital, Torrance.

### Fridays

8:00 a.m., Lecture Room, A Floor, Health Sciences Center, UCLA. CRMP Area IV.

8:30 a.m., Room M104, Stanford University Medical Center, Stanford.

8-9:00 a.m., Lecture Hall, Childrens Hospital of Los Angeles.

Infectious Disease Grand Rounds. 10:00 a.m., Auditorium, Childrens Division Building, Los Angeles County-USC Medical Center, Los Angeles. USC.

## PSYCHIATRY

June 26-28—**Comparative Psychotherapies.** USC Division of Postgraduate Psychiatry at Sahara Tahoe Hotel, Lake Tahoe. Friday-Sunday. \$35. Contact: Donald

F. Naftulin, M.D., Director, Division of Postgraduate Psychiatry, USC. (213) 225-1511, ext. 336.

September 23-26—**American Academy of Psychosomatic Medicine.** St. Francis Hotel, San Francisco. Wednesday-Saturday. Contact: Edwin Dunlop, M.D., 150 Emory St., Attleboro, Mass. 02703. (617) 222-2600.

September 29-October 20 — **Conflict: Man Against the System.** UCLA. Tuesday evenings. Psychiatric discussions of character disorders as shown in films.

September 29-December 15 — **Psychodynamics of Behavior.** UCLA. Tuesday evenings.

October 2-4 — **Marriage Counseling Program.** UCSF at St. Francis Hotel, San Francisco. Friday-Sunday.

October 17-18—**Depression.** UCSF at Mendocino State Hospital, Talmage. Saturday-Sunday.

October 19-23—**Group Therapy.** UCSF at VA Hospital, San Francisco. Monday-Friday.

October 24—**Approaches to Self Destruction.** UCSF. Saturday.

## **RADIOLOGY—PATHOLOGY**

October 3 — **Scintillation Camera Workshop.** UCSF. Saturday.

Continuously—**Principles and Clinical Uses of Radioisotopes.** UCSF. Fundamentals for the proper understanding and use of radioactivity in clinical medicine. Training in diagnostic and therapeutic uses of radioisotopes. Normal period of training: 3 months. Two part course: Part A, Basic Fundamentals; Part B, Clinical Applications.

Continuously — **Mammography.** UCSF Mammography Section, Department of Radiology. Three days weekly, beginning with Tuesday. Call several days in advance. Contact: Richard H. Gold, M.D., Mammography Section, Department of Radiology, UCSF. (415) 666-1918.

## **Grand Rounds—Radiology**

### **Fridays**

Neuroradiology Grand Rounds. 9:30 a.m., held alternately at Stanford University Hospital and Neurology Conference Building 7, V.A. Hospital, Palo Alto, STAN.

## **SURGERY—ANESTHESIOLOGY**

June 25-27—**1970 Stanford Ophthalmology Conference.** STAN. Thursday-Saturday. Diseases of conjunctiva and cornea, retina and choroid, practical aspects of ocular physiology and bacteriology. \$100. 17 hrs. Contact: Jerome Bettman, M.D., Division of Ophthalmology, A227, Dept. of Surgery, STAN.

July 1-August 29—**Stanford Basic Course in Ophthalmology.** STAN. Two months. Sections in Biochemistry, Physiology, Embryology and Genetics, Microbiology and Immunology, Neuro-ophthalmology and Neuroanatomy, Optics and Theory of Refraction, Motility, Pharmacology and Toxicology. \$550. 227½ hrs. Contact: Jerome Bettman, M.D., Division of Ophthalmology, A227, Dept. of Surgery, STAN.

July 5-17—**Temporal Bone Dissection Course.** Los Angeles Foundation of Otolaryngology, Los Angeles. Two week course demonstrating multiple approaches to structures of the temporal bone. Televised surgery correlated with dissections, lectures and motion picture demonstrations. Dissection in temporal bone laboratory over closed circuit television, student supervision. \$1,000 Otolaryngologists, \$500 Residents. 106 hrs. Course repeated in October, 1970. Contact: Jack L. Pulec, M.D., Los Angeles Foundation of Otolaryngology, 2130 W. Third St., Los Angeles 90057. (213) 483-4431.

July 18—**Clinical Electronystagmography Course.** Los Angeles Foundation of Otolaryngology, Los Angeles. Saturday. Physicians urged to bring ENG Technician for special instruction. Anatomy and Physiology of Vestibular System, Demonstration of Technique of Vestibular Stimulation and ENG Recording and Calculation, Significance of and Interpretation of Electronystagmogram, Discussion of Cases, Vistas in Vestibular Investigation. \$60. 6½ hrs. Contact: Jack L. Pulec, M.D., Los Angeles Foundation of Otolaryngology, 2130 W. Third St., Los Angeles 90057. (213) 483-4431.

July 30-August 1—**Strabismus Conference.** PMC Department of Ophthalmology at PMC. Thursday-Saturday. Surgical Diagnosis and Treatment, Follow-up. Emphasis of surgical technique through motion picture. \$125. Contact: Wayne L. Erdbrink, M.D., Director of Residency Training, Dept. of Ophthalmology, PMC.

August 3-5—**The Knee in Sports.** American Academy of Orthopaedic Surgeons at Hilton Hotel, San Francisco. Monday-Wednesday. \$150. 20 hrs. Contact: Fred H. Behling, M.D., 300 Homer Avenue, Palo Alto 94301. (415) 321-4121.

August 19-23—**Advanced Seminar in Urology.** UCLA at UCLA Residential Conference Center, Lake Arrowhead. Wednesday-Sunday.

August 26-28—**Keratoplasty Conference.** PMC Department of Ophthalmology at PMC. Wednesday-Friday. Planned for practicing ophthalmologists, improvement of surgical technique in corneal transplants and other aspects of keratoplasty. \$125. Contact: Wayne L. Erdbrink, M.D., Director of Residency Training, Dept. of Ophthalmology, PMC.

October 4-9—**American Society of Plastic and Reconstructive Surgery.** Century Plaza Hotel, Los Angeles. Sunday-Friday. Contact: Peter Randall, M.D., Gen. Sec., 18 Laughlin Lane, Philadelphia 19118. (215) 247-1797.

October 18-30—**Temporal Bone Dissection Course.** See Surgery, July 5-17.

## **Grand Rounds—Surgery**

### **Wednesdays**

7:15 a.m., Auditorium, Kern County General Hospital, Bakersfield. CRMP Area IV.

1st and 3rd Wednesdays. 11:00 a.m., Auditorium, Brown Building, Mount Sinai Hospital, Los Angeles. CRMP Area IV.

### **Thursdays**

Neurology and Neurosurgery Grand Rounds. 11:00-12:15. Room 663, Science Building, UCSF.



## **Fridays**

1-2:00 p.m., Auditorium, Orange County Medical Center, Orange. UCI.

Neurosurgery. 11:15 a.m., held alternately at Stanford University Hospital and Neurology Conference Building 7, V.A. Hospital, Palo Alto, STAN.

## **Saturdays**

8:00 a.m., Auditorium, 1st floor, University Hospital of San Diego County, San Diego. UCSD.

9:00 a.m., Room 73-105, Health Sciences Center, UCLA. CRMP Area IV.

8:30 a.m., Assembly Room, Harbor General Hospital, Torrance. CRMP Area IV.

## **OF INTEREST TO ALL PHYSICIANS**

June 17—**Income Maintenance Predicated on Reproductive Responsibility: A New Approach To The Prevention of Mental Illness Due to Ignorance, Poverty, and Overcrowding.** Agnews State Hospital, San Jose. Wednesday. 1½ hrs. Contact: J. Elizabeth Jeffress, M.D., Agnews State Hospital, San Jose 95114. (408) 262-2100.

June 21-25 — **American Medical Association.** Palmer House, Chicago. Sunday-Thursday. Contact: Ernest B. Howard, M.D., Exec. Vice-Pres., AMA, 535 N. Dearborn St., Chicago 60610. (312) 527-1500.

July 15—**The Tenth Annual UCLA Seminar for General Practitioners.** UCLA at UCLA Residential Conference Center, Lake Arrowhead. Wednesday-Sunday.

July 5-6—**Short Course on Liquid Scintillation Counting for Radioisotope Measurement.** UCSF. Sunday-Monday.

July 7-10—**International Conference on Organic Scintillators and Liquid Scintillation Counting.** UCSF. Tuesday-Friday.

July 19—**Medical Management and Rehabilitation of the Handicapped: A Symposium for Medical Assistants.** UCSF. Sunday. \$12.50.

### **CMA Postgraduate Institutes and Circuit Courses**

June 18-20—**Sacramento Valley Counties Regional Postgraduate Institute.** CMA, UCLA and Sacramento County Medical Society at Cal Neva Lodge, North Lake Tahoe. Thursday-Saturday. Cerebral Vascular Disease including Rehabilitation and the Surgical and Medical Management of Cardiac Disease, Delivery of Health Care in the '70s. \$20. 12 hrs. Contact: CMA.

July 20-24 — **Hospital Information Systems: Techniques and Applications.** University of Southern California at Olin Hall of Engineering, University of Southern California. Monday-Friday. Emphasis on use of computer techniques in intensive care units, diagnos-

tic aids, clinical laboratories, patient care, medical research, multiphasic screening. \$275. 40 hrs. Contact: William D. Campbell, Noncredit Programs, Administration Building, Room 355, University of Southern California, University Park, Los Angeles 90007. (213) 746-2418.

August 15-26 — **Thirteenth Annual Postgraduate Refresher Course in Honolulu and Kauai.** USC and the University of Hawaii School of Medicine at Royal Hawaiian Hotel, Tripler General Hospital, Kauai Surf Hotel, Surf Rider Hotel, and Princess Kaiulani Hotel. One and a half weeks. Shock, Adolescence, Spatial ECG, Pharmacology, Psychiatry, Orthopedics, Endocrinology, Surgery, Cardiology, Arrhythmias, Obstetrics and Gynecology, Obesity, Neurology, Emergency Care, Diabetes, Medicine, Pediatrics. 26 hrs. Contact: USC.

August 23-27 — **American Society for Pharmacology and Experimental Therapeutics.** Stanford University, Stanford. Sunday-Thursday. Contact: Ellsworth B. Cook, Ph.D., 9650 Rockville Pike, Bethesda, Md. 20014. (301) 530-3200.

September 10-12—**National Conference for Pharmacy.** UCSF. Thursday-Saturday.

September 20-23 — **American Association of Medical Clinics.** St. Francis Hotel, San Francisco. Sunday-Wednesday. Contact: Edwin P. Jordon, M.D., P.O. Box 58, Charlottesville, Va. 22902. (703) 295-9470.

September 23-26—**American Academy of Psychosomatic Medicine.** See Psychiatry, September 23-26.

September 25-27 — **Prevention of Iatrogenic Disease.** California Medical Association—California Nurses Association—California Council of Hospital Pharmacists. Disneyland Hotel, Anaheim. Friday-Sunday. 12 hrs. Contact: Eugene Miller, M.D., CMA.

September 28-October 2—**American Academy of General Practice.** Civic Auditorium, Brooks Hall, Fairmont and Mark Hopkins Hotels, San Francisco. Monday-Friday. Contact: Mac F. Cahal, M.D., Volker Blvd. at Brookside, Kansas City 64112. (816) 531-0377.

September 30-October 1 — **American Medical Association—Thirtieth Annual Congress on Occupational Health.** Century Plaza Hotel, Los Angeles. Wednesday-Thursday. Contact: Louis R. Skiera, Asst. Dir., 535 N. Dearborn St., Chicago 60610. (312) 527-1500, ext. 482.

October 2-3—**Western Industrial Medical Association.** Century Plaza Hotel, Los Angeles. Friday-Saturday. Contact: B. H. Bravinder, Exec. Dir., WIMA, 2180 Milvia St., Berkeley 94704. (415) 845-3355.

October 4 — **A Symposium for Medical Assistants.** UCSF. Sunday.

October 6-December 1—**Evening Lectures in Medicine.** UCSF at Oakland Hospital, Oakland. Tuesday evenings, except November 3.

October 21-24—**National Hemophilia Foundation.** Beverly Hilton Hotel, Beverly Hills. Wednesday-Saturday. Contact: John Walsh, Vice-Pres., NHF, 25 W. 39th St., New York 10018. (212) 279-8397.



October 24-26—**American Academy of Clinical Toxicology**. Jack Tar Hotel, San Francisco. Saturday-Monday. Medical and legal aspects of clinical toxicology, drug abuse, general session. \$25 members, \$35 non-members. 24 hrs. Contact: Eric G. Comstock, M.D., Exec. Dir., P.O. Box 2565, Houston 77001. (713) 524-7547.

October 30-November 1—**Immunology**. UCSF. Friday-Sunday.

October 30-November 2 — **Association of American Medical Colleges**. Biltmore Hotel, Los Angeles. Friday-Monday. Contact: Robert C. Berson, M.D., 1346 Connecticut Ave. NW, Washington, D.C. 20036. (202) 466-5100.

Continuously—**Audio-Digest Foundation**. A non-profit subsidiary of CMA. Twice-a-month tape recorded sum-

maries of leading national meetings and surveys of current literature. Services by subscription in: General Practice, Surgery, Internal Medicine, Ob/Gyn, Pediatrics, Anesthesiology, Ophthalmology. Catalog of lectures and panel discussions in all areas of medical practice also available. Contact: Mr. Claron L. Oakley, Editor, 619 S. Westlake Ave., Los Angeles 90057.

Continuously — **UCLA's Medical Television Network**. Programs available on videotape, 8 mm. film cartridge and 16 mm. film. Programs of 30 minutes or less, supplemented by study guides, bibliographies, and self-testing devices. Of educational value to physicians, nurses, and allied health personnel. Contact: Richard Getz, Exec. Dir., Medical Television Network, University Extension, UCLA, Los Angeles 90024. (213) 825-2071.

### THE ELECTROENCEPHALOGRAM IN UREMIC COMA

"Of all the neurological laboratory studies, the electroencephalogram could be considered the most helpful in patients in uremic coma. If focal brain wave abnormalities are found, these, in contradistinction to focal clinical signs, are probably significant and warrant fairly intensive study regarding the possible existence of other brain disease.

"The electroencephalogram is usually a straightforward, fairly consistent thing in uremic coma—no focal signs but rather the picture of a diffuse metabolic suppression. By this we mean that there is a progressive loss of the normal alpha rhythms bilaterally; then there's a superimposed rapidly increasing diffuse slowing. Eventually there's even a loss of brain wave reactivity to photic or other stimulation, but again an obvious diffuseness about this."

—THOMAS W. WALLACE, M.D., Cleveland  
Extracted from *Audio-Digest Internal Medicine*, Vol. 16. No. 5, in the Audio-Digest Foundation's subscription series of tape-recorded programs.

# BOOK REVIEWS

CALIFORNIA MEDICINE does not review all books sent to it by the publishers. A list of new books received is carried in the Advertising Section.

**ORGANIZATION AND ADMINISTRATION OF HEALTH CARE—Theory, Practice, Environment**—Richard L. Durbin, A.B., M.B.A., M.P.A., Administrator, Temple University Hospital; Associate Professor, Temple University School of Business, Philadelphia; and W. Herbert Springall, A.B., M.P.H., Associate Administrator, Temple University Hospital; Assistant Professor of Hospital Administration and Chairman, Department of Health Care Management, Temple University College of Allied Health Professions, Philadelphia. The C. V. Mosby Company, 3207 Washington Boulevard, St. Louis, Mo. (63103), 1969. 248 pages, 51 illustrations, \$9.85.

This book will be of interest to those concerned with the administration and management of hospitals and university medical centers. It will also be of value to health planners and physicians with major staff responsibilities in hospitals and medical centers. Many, however, will find much to view critically.

The book has five sections: "Spectrum of Administration," "Environment and Organization," "Resources and Application," "Implementation," and "Projection." The most interesting are the chapters on hospital organization and reorganization in the section "Environment and Organization" and the chapter on systems in "Resources and Application."

The authors develop their concepts regarding the use of resources through the systems approach, and making these resources available to program managers. The resource elements include the patient care system (nursing, social service, operating room, intensive care, emergency rooms and others); professional service department system (pharmacy, laboratories, x-ray, physical therapy, anesthesiology and others); logistics system (this system includes purchasing, storeroom, laundry, dietary, central supply); business and finance system (this includes business office, accounts payable, accounts receivable, payroll, gift shop); quality control system (systems and procedures, information desk, switchboard, medical records, duplicating, admitting, mail room); environmental services system (housekeeping, physical plant, transportation); security and medical legal system (security, medicolegal) and personnel and education system (personnel, in-service training, training and retraining and contracts). The hospital administrator is ultimately responsible for placing these resources at the service of the program managers. It is the program manager's responsibility to utilize the various program elements to meet the needs of the patient. In addition to this approach to resource allocation and organization, the authors are strong advocates of decentralization of decision making. The program managers are given more authority and responsibility under this form of organization. They are also held accountable for their actions.

The chapter on "Programs" is not as clear or stimulating as that on "Systems." Chapters on "Nursing" and

"Quality Control" should be of interest to nursing staff, as well as hospital management and medical staff. Some of the other sections are overly simple or tedious in reiterating accepted concepts.

The final chapter, "Beyond Traditional Patterns," includes some interesting ideas, such as hospital service corporations, but it is disappointing in that it does not deal broadly with the problems of health care organization.

In summary, this is an interesting, stimulating, but uneven book by two leaders in the field of hospital and medical center administration. It deals with problems of administration and management in hospitals and university medical centers. It will be of most interest to those directly concerned with administration and management of these institutions.

PHILIP R. LEE, M.D.

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**A TEXTBOOK OF X-RAY DIAGNOSIS**—By British Authors—In Six Volumes—Fourth Edition—Vol. 1—Head and Neck—Edited by S. Cochrane Shanks, C.B.E., M.D., F.R.C.P., F.F.R., Consulting Radiologist, University College Hospital, London; and Peter Kerley, C.V.O., C.B.E., M.D., F.R.C.P., F.F.R., Consulting Radiologist, Westminster Hospital and the National Heart Hospital, London. W. B. Saunders Company, West Washington Square, Philadelphia, Pa. (19105), 1969. 688 pages, \$21.00.

The publication of the 4th edition of this classic textbook by British authors brings the work up to date and renews its value to diagnostic radiologists. To incorporate fresh material developed in the decade since the 3rd edition, the editors have enlarged the book from five volumes to six. The first volume includes the head and neck with sections on the central nervous system, the teeth and jaws, the eye, the paranasal sinuses and the ear and temporal bone.

Except for the chapter on the eye, the book has been extensively re-written. New material has been added on brain scans, ultra-sound, orbital venography and stereotactic surgery. There is an excellent new chapter on the choice of radiological methods in the management of neurological conditions. Disappointingly little has been introduced on subtraction techniques and tomography, particularly on tomography of the temporal bone.

The book suffers considerably from poor detail on some of the reproductions of the radiographs. The point of the illustration is not always easily discernible. However, the book is concise and thorough. Now that it is up to date, it will again be valuable to radiology residents as a comprehensive textbook for study and to practicing radiologists as an authoritative reference.

ROBERT N. BERK, M.D.



AN INTRODUCTION TO THE HISTORY OF GENERAL SURGERY—Richard Hardaway Meade. W. B. Saunders Company, West Washington Square, Philadelphia, Pa. (19105), 1968. 403 pages, \$17.00.

In a somewhat disarming preface, the author contends that of the many histories of surgery "written during the last few centuries" the majority have been devoted primarily to a discussion of the surgeons as individuals rather than to the discipline of surgery itself. Therefore it is his intent "to sketch the major advances since the *Smith Papyrus*." Further, but with a few exceptions, he has not covered the specialties after they became recognized as such. Since the advances in thoracic surgery have been the work of men who considered themselves general surgeons, the author limits his discussion of this field to the period prior to World War II. However, "because of the widespread interest in human heart transplantation," he has included a chapter on the history of organ transplantation authored by Dr. James D. Hardy.

The text itself fulfills more or less the author's stated aims. It concentrates for the most part on surgery itself, discussing the advances in the various subject fields in terms of procedures and results. Naturally such an approach puts the emphasis on the post-anesthetic and post-Listerian periods of surgery in this later nineteenth century era. The text is on the whole very reliable and informative. Nonetheless the approach, unless handled conceptually, has its defects. Rather than a history, it becomes a chronicle of events, gives undue emphasis to priorities, and makes very dry reading. All these defects are evident, although some relief is provided in the individual sections by the discussions of preliminary developments of earlier times. But it is in these earlier periods, say prior to the nineteenth century, that the work is very unsatisfactory: the text abounds in errors and misstatements. Latin titles of books are often incorrectly transcribed; quotations given from the wrong editions; wrong titles attributed to authors, and many other curious and inaccurate transpositions. Obviously a great number of these errors has entered the work through too great a reliance on secondary, and often tertiary, sources.

Nonetheless, bearing in mind the *caveat* as to the unsatisfactory aspects of the text on the earlier periods of the history of surgery, the work as a whole is most useful and informative. Younger surgeons will read it with profit, especially for the more recent developments of their craft during the epoch when surgery made its greatest advances.

J. B. DE C. M. SAUNDERS, M.D.

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GENETICS AND COUNSELING IN MEDICAL PRACTICE—Leonard E. Reisman, M.D., Associate Professor of Pediatrics and Pathology, The Jefferson Medical College of Philadelphia; and Adam P. Matheny, Jr., Ph.D., Assistant Professor of Pediatrics and Chief Psychologist, Children and Youth Project, University of Louisville School of Medicine. The C. V. Mosby Company, 3207 Washington Boulevard, St. Louis, Mo. (63103), 1969. 215 pages, 86 illustrations, \$12.75.

Reisman and Matheny in their preface to their book *Genetics and Counseling in Medical Practice*, state the "purpose of this book is to provide a broad coverage of information that the family physician can use to help people seeking genetic advice." They further state the book is intended as a primer in genetic counseling to correct a discrepancy between what is known about genetic disorders and the extent to which that knowledge is applied clinically.

These are much needed objectives and the discussions and illustrations of specific genetic disorders will certainly prove helpful. Unfortunately the genetic mechanisms and terminologies are too esoteric for the family physician who has not obtained special training in genetics.

It is doubtful to me that the average family physician can turn to a section of this book and readily understand what he reads. The book repeatedly uses genetic terms without defining them and also fails to provide a glossary which would define the terms. Though obviously this book wasn't intended as a full treatise on genetics, one chapter to provide the basic principles of genetics and a simplified presentation of what really happens in normal mitosis and meiosis and a few examples of aberrant mechanisms should be a *must read* chapter at the beginning of the book.

Such a chapter plus a glossary of terms would enable a family physician to quickly review what he needs to know to understand the specific discussions. Without such additional information readily available in the book the family physician not already well oriented to genetics will find the book hard to understand and therefore less useful than it could have been.

J. H. BAIER, M.D.

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PROGRESS IN COMMUNITY MENTAL HEALTH—Volume I—Edited by Leopold Bellak, M.D., and Harvey H. Barten, M.D. Grune & Stratton, Inc., 381 Park Avenue South, New York, N.Y. (10016), 1969. 272 pages, \$11.75.

Although this expensive multiauthored volume will probably be most useful to mental health professionals, it should be of interest to a broad group including health professionals in general, paraprofessional workers in the field of community mental health, and some lay readers who, for one reason or another, are invested in this field. A critique here of each of the book's 12 independently authored chapters does not seem feasible. The primary focus of this review, therefore, will remain general, including only a few comments about specific chapters.

The editors in the Foreword outline the charge given to their contributors, namely, to accomplish a critical review of their respective field, as well as to provide projections beyond today to what can be anticipated in community mental health practice in the future. This goal has been generally achieved. The shared emphasis of the authors upon review and prediction provides a consistent theme which succeeds in weaving the chapters together in an interesting fashion.

The book's three major divisions, namely, Organization and Objectives, Direct Services, and Indirect Services, will for the community practitioner prove to be a reasonable format although there may be some initial confusion for other readers about the concepts of direct versus indirect services.

The section on Organization and Objectives provides an excellent orientation to the field of community mental health. The chapter in this section written by Dr. Stanley Yolles, Director, National Institute of Mental Health, provides a succinct and insightful history of developments, trends, and factors which influenced the development of the community mental health center concept. Dr. Alan Levenson's contribution in this division of the book entitled "Organizational Patterns and Community Mental Health Centers" is reassuring and informative in its description of the variety of different forms and models of community mental health centers which communities have developed through their planning. This would seem to acknowledge not only the individual and different needs of communities, but also the fact that the community mental health field is still in the vital process of developing and evaluating different interventions as well as programs. This focus upon unresolved problems and the challenges of the field is continued in the probing presentation of Dr.



David Mechanic's chapter entitled "Sociological Issues in Mental Health." He considers complex issues such as societal responses to illness behavior, priorities for interventions, implications for community mental health planning raised by chronic psychiatric illness, and general factors related to the "sick role."

The content of the Direct Services division focuses upon treatment approaches for identified psychiatric problems. The chapters in this section on brief psychotherapy, group approaches, family therapy, rehabilitation, and services for children each provide a commendably comprehensive and thoughtful review of these areas with particular attention accorded to innovative approaches and modifications designed to meet the special aspects of community practice. The bibliographies in this section, particularly the one on Brief Psychotherapy, have been compiled with care. In fact, the references cited throughout the volume provide a good introduction to some of the basic literature in a field that has recently been caught up in an information explosion.

The final division of the book, Indirect Services, includes an excellent chapter on "Prevention of Mental Illness" by Dr. William M. Bolman. His consideration of differing concepts of prevention in the mental health field is helpful, and this is enhanced by the presentation of several examples of preventive programs for children and young people including preschool, school entry, and school exit projects.

Although the chapter on "Mental Health Consultation" by Dr. Howard Kern, Jr., is rambling, the author does make an important contribution in his description of the consultation as a mutually educative process which requires that the consultant become comfortable with multiple, shifting roles.

Dr. Bellak's prediction that his chapter on "Community Mental Health as a Branch of Public Health" would arouse violent reactions does not assuage concern about its alarming content. It is certainly true that mental health programs in communities need to be aware of and concerned about individuals whose emotional problems may adversely affect others in the community. However, Dr. Bellak's focus upon screening, isolation, enforced treatment, and special control legislation for this group would indeed be an ominous projection of things to come. This "quarantine philosophy" is certainly not advocated by contemporary community mental health practitioners. In view of the many significant and vital contributions from the public health field to the community mental health model, Dr. Bellak's highly controversial proposal seems most unfortunate. It is regrettable that the division on Indirect Services did not include a chapter on program evaluation since the need to assess the result of interventions is of such primary importance and urgency in the field. However, it is probable that the editors intend to devote subsequent volumes to this subject.

Although this book can and will be viewed critically with reference to some of its sections, it certainly does provide a timely and informed prospectus of the progress being made and anticipated in the field of community mental health.

M. ROBERT HARRIS, M.D.

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**COOKING FOR YOUR CELIAC CHILD—DIETARY MANAGEMENT IN MALABSORPTION DISORDERS**—Charlotte Baum Sheedy and Norman Keifetz. The Dial Press, Inc., 750 Third Avenue, New York, N.Y. (19017), 1969. 244 pages, \$5.95.

A gluten-free diet for a celiac child is one of the more complicated diets. In everyday practice the pediatrician often gives the mother a list of foods to avoid but seldom

has time to discuss at great length what foods to use. *Cooking For Your Celiac Child* can be highly recommended by the doctor as an adjunct.

By providing a ready reference in the section listing permitted and forbidden foods, this book will answer the mother's questions that surely will come up every day. There are a large number of varied and ingenious recipes that will enable the mother to take an active part in the most important phase of the child's care. Many recipes for "treats" make what may otherwise be a monotonous diet even enjoyable. The recipes are simple and directions are easy to follow. If the child were able to read, he too, would recommend the book to his mother.

RAYMOND LEE, M.D.

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**PICTORIAL HISTORY OF PSYCHOLOGY AND PSYCHIATRY**—A. A. Roback and Thomas Kiernan. Philosophical Library, Inc., 15 East 40th Street, New York, New York (10016), 1969. 294 pages, \$12.50.

In illustrated histories it is generally assumed that the text explains the illustrations while the illustrations illuminate the text. This mutual relationship does not exist in the book here reviewed. Here the two, text and illustrations, simply coexist without any noticeable interdependence. Thus, on page 71 there is extensive text about Carl Stumpf, while on the same page an illustration shows a contemporary, Edward Spranger, who has no relationship whatsoever with Carl Stumpf. Perhaps there was no picture of Stumpf available, but in that case it might have been preferable to leave the page unillustrated. Similarly, incongruities abound in the volume, and beyond this, many of the illustrations are almost totally irrelevant to the subject, the history of psychiatry. It must be admitted that the text, if it were published without illustrations, would be reasonably interesting, though a somewhat peculiar history of psychology and psychiatry, especially as far as the beginning of Graeco-Roman times are concerned. Here, as elsewhere, throughout the volume the reader misses footnotes and the customary references that usually accompany a work of this nature. This absence of the so-called "scholarly apparatus" calls attention to another omission which is quite serious and serves as a continuous irritant to the reader of the book. This omission refers to the identification of the authors, A. A. Roback and Thomas Kiernan, about whose personal and professional provenance we remain totally uninformed. Even the dust cover, which generally contains information about authors, is silent on this subject, and restricts itself to euphemistic prose about the novelty of the book.

Like most large illustrated works, this one, too, will look decorative on a coffee table, and will lend a flavor of erudition to the psychiatrist's waiting room; and it would therefore be a useful, though not intellectually taxing, gift selection for a psychiatric colleague.

ILZA VEITH, M.A., Ph.D.

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**THE TREATMENT OF BURNS**—Second Edition—Curtis P. Artz, M.D., F.A.C.S., Professor of Surgery and Chairman of the Department, Medical College of South Carolina, Charleston, formerly Commanding Officer and Director, U.S. Army Surgical Research Unit, Brooke Army Medical Center, Fort Sam Houston, Texas; and John A. Moncrief, M.D., F.A.C.S., Colonel, Medical Corps, Commanding Officer and Director, U.S. Army Surgical Research Unit, Brooke Army Medical Center, Fort Sam Houston, Texas. W. B. Saunders Company, West Washington Square, Philadelphia, Pa. (19105), 1969. 393 pages, \$14.50.

This is an expanded and revised edition of the classic monograph on burn treatment by Curtis Artz and Eric Reiss. The current authors, Colonel Artz and Colonel John Moncrief have each served as commanders of the

U.S. Army Surgical research unit at Brooke Army Hospital, and the presentation relies heavily but not entirely on the experiences in this burn unit.

The new chapter on pathology of burns by guest author Dr. Carl Teplets presents much material not published before. The demanding requirements of performing an autopsy on a burn victim are explained. While the author notes that most pathophysiologic changes resulting in death during the first few days after burning are not clarified by light microscopic examination, pulmonary edema and congestion and inflammatory changes may be prominent. Much space is devoted to methods of examining the burn wound and evaluating its contribution to death from sepsis. The relative paucity of clinical and post mortem signs of bacteriologic overgrowth in patients dying with pseudomonas burn sepsis is contrasted with the abundant evidence of bacterial dissemination in cases of staphylococcal sepsis. The author feels that burn wound infection was the primary cause of death in most instances but with pulmonary problems contributing significantly in many cases. He notes that most of the Army burn patients were between 16 and 40 years of age and they all were free of antecedent disease. Findings in the respiratory tree and abdominal viscera are discussed, notably those in the stomach and kidney.

The chapter on general immediate care follows fairly closely the corresponding chapter in the first edition, and is well organized. A warning is made about the over use of antibiotics and the overgrowth of resistant organisms. Again the importance of the initial reaction of the patient and his family to a courteous, friendly and interested staff is stressed.

A new chapter on office treatment of burns provides guidelines useful to any medical practitioner who may be called on for emergency treatment.

The pathophysiology of fluid loss in burns is discussed at some length. The various formulae used today for fluid replacement are considered, and the authors note that all of their proponents have comparably successful results. The clinician is therefore advised to become familiar with any one method.

The chapter on initial local care has been expanded, with sections on the use of sulfamylon and silver nitrate as topical antibacterial agents. Advantages and problems with each method are discussed in a refreshingly unbiased presentation.

An informative new chapter on anesthesia for the severely burned patient by Dr. Burton Epstein includes advice on airway management as well as a critique of various anesthetic agents. It discusses management of problems specific to burns, such as blood loss and heat loss. The discussion of the repair of full thickness burns points out that when the newer local anti-bacterial treatments are used, the burn eschar remains adherent for a much longer time than it did with the older methods of treatment. The authors therefore recommend surgical removal of the eschar if it has not begun to loosen by the thirtieth day. There is further discussion of methods of removal of the eschar and preparation of the recipient sites for grafting, followed by a description of the use of various dermatomes. The use of homografts is also discussed.

Electrical burns were discussed in some detail and the short but very useful section on chemical burns brings together much information from rather obscure references in the literature. This section alone would make the book very useful in the hospital emergency room.

Burns of specific area are again discussed. While some clinicians might take issue with the authors' recommenda-

tions of generous removal of cartilage from the burned ear, the discussion of respiratory burns and burns of the hand are very instructive and reflect the authors' enormous experience.

A new chapter on burns in children points out the susceptibility of the infant to problems of fluid overloading and dehydration. The increased energy requirements of the infant are discussed along with the problems engendered by the relative thinness of the skin of children. Respiratory burns, especially where tracheostomies are required, are particularly difficult problems in children and are covered in a very interesting and instructive manner.

Nursing care and psychological considerations are discussed in another separate chapter. Again the authors stress the great value of informed and sympathetic nursing care in the treatment of the burned patient. The chapter on metabolic response and nutrition has been revised. The problems of protein loss and negative nitrogen balance is clarified and there is an interesting section on the response of the endocrine glands to burns.

The single greatest change in the management of burns in recent years has had to do with the treatment of infection. This is covered in a separate chapter which emphasizes control of the burn wound flora with the use of dressings and anti-bacterial substances. The futility of trying to control bacteria on the burn wound with systemic antibiotics alone is pointed out; the authors recommend the use of antibiotics only to minimize the spread of bacteria to unburned portions of the body. The insidious character of the gram negative infection is contrasted with the more easily recognizable gram positive organism infection.

Chapters on the complications of burns and burn therapy, particularly those involving the respiratory tract and gastrointestinal ulcerations should be familiar to all physicians dealing with burns. The prevention and treatment of contractures and the treatment of fractures associated with burns are also informative. A short discussion of treatment of burns in a disaster concludes this excellent reference book.

In summary this is a book which deserves to be read by anyone who comes into contact, however slight, with the burned patient, and as such should have a place in every hospital and emergency room library.

RICHARD L. DAKIN, M.D.

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ARROWS OF MERCY—Philip Smith. Doubleday & Company, Inc., 277 Park Avenue, New York, N.Y. (10017), 1969. 244 pages, \$5.95.

*Arrows of Mercy* gives an excellent review of curare's development from its early days, as used in the jungle by the natives, to its revolutionizing effect upon modern clinical anesthesia. Mr. Smith has shown the importance of curare's contribution to surgery and the many great benefits which have been derived from its use. He shows the difficulties in obtaining the drug, its purification, and the problems of standardization.

The struggle to bring a new drug to life is both frustrating and discouraging. Mr. Smith gives credit to the men who worked hard to obtain its acceptance. He briefly describes the evolution of surgery from the stone age to its modern day practice and the continual attempt to render the patient pain-free during a surgical procedure. The change which curare brought to surgery was tremendous. Deep anesthesia for muscle relaxation was no longer necessary and the mortality rate decreased.

*Arrows of Mercy* is well written. It is presented in an entertaining manner and I am sure that most individuals of the medical, paramedical and lay fields will find it enjoyable and informative.

NORMAN LEVIN, M.D.





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- Introduction to the History of General Surgery, *An, Meade* (Jun) 88
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# BOOKS RECEIVED

**PROGRESS IN CLINICAL CANCER**—Vol. IV—Edited by Irving M. Ariel, M.D., F.A.C.S., Associate Clinical Professor of Surgery and Attending Surgeon, New York Medical College, Flower and Fifth Avenue Hospitals; Attending Surgeon, Pack Medical Group, New York, N.Y. Grune & Stratton, Inc., 757 Third Avenue, New York, N.Y. (10017), 1970. 405 pages, \$29.75.

**MORE THAN SKIN DEEP**—Thomas H. Sternberg, M.D., Professor and Chairman, Division of Dermatology, School of Medicine, University of California, Los Angeles. Doubleday & Company, Inc., 277 Park Avenue, New York, N.Y. (10017), 1970. 330 pages, \$7.95.

**MODERN TREATMENT**—Vol. 7, No. 1, January 1970—Treatment of Cardiac Arrhythmias—Guest Editor, Noble O. Fowler, M.D. Harper & Row, Publishers, Inc., 49 East 33rd Street, New York, N.Y. (10016), 1970. 237 pages, \$20.00. Sold by subscription, published bimonthly.

**SKIN SURGERY**—3rd Edition—Edited by Ervin Epstein, M.D., Associate Clinical Professor of Dermatology, University of California Medical School, Formerly Associate Clinical Professor of Medicine (Dermatology), Stanford University Medical School, Chief of Dermatology and Syphilology at Highland-Alameda County Hospital, Consultant to Oakland Area Veterans' Hospital. Charles C Thomas, Publisher, 301-327 East Lawrence Avenue, Springfield, Ill. (62703), 1970. 647 pages, \$48.50.

**MODERN SURGERY**—Edited by Richard H. Egdahl, M.D., Professor and Chairman, Department of Surgery, Boston University Medical Center; and John A. Mannick, M.D., Professor of Surgery, Boston University Medical Center. Grune & Stratton, Inc., 757 Third Avenue, New York, N.Y. (10017), 1970. 1194 pages, \$19.75.

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**CURRENT PROCEDURAL TERMINOLOGY**—2nd Edition—Burgess L. Gordon, M.D., Editor; William R. Barclay, M.D., Director, Division of Scientific Activities; and Charlotte Fanta, B.S., Associate Editor. American Medical Association, 535 North Dearborn Street, Chicago (60610), 1970. 368 pages, \$2.00.

**MEDICINE AND STAMPS**—Edited by R. A. Kyle, M.D. and M. A. Shampo, Ph.D. Published by the American Medical Association, 535 North Dearborn Street, Chicago (60610), 1970. 216 pages, \$1.00.

**CLINICAL GASTROENTEROLOGY** — Howard M. Spiro, M.D., Professor of Medicine, Yale University School of Medicine; Attending Physician, Yale-New Haven Hospital, New Haven, Conn.; Consultant in Gastroenterology, Hospital of St. Raphael, New Haven; U.S. Veterans Administration Hospital, West Haven; Griffin Hospital, Derby; William W. Backus Hospital, Norwich, Conn. The Macmillan Company, 866 Third Avenue, New York (10022), 1970. 1011 pages, \$35.00.

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